Cisapride (Monograph)

Drug class: Prokinetic Agents
- Benzamides
ATC class: A03FA02
VA class: GA900
Chemical name: cis-4-Amino-5-chloro-N-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxy benzamide
Molecular formula: $C_{23}H_{29}ClFN_3O_4$
CAS number: 81098-60-4

Medically reviewed by Drugs.com on Jan 22, 2025. Written by ASHP.

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Warning

Notice: On March 23rd, 2000, Janssen Pharmaceutica announced the withdrawal of the GI motility stimulant cisapride (Propulsid) from the US market, as of July 14th, 2000. This announcement resulted from information regarding accumulating data on an association between use of cisapride and the development of numerous cases of serious cardiac arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsades de pointes, QT-interval prolongation) and death in certain patients.

From July 1993 (when the drug was approved for use in the US) through December 1999, 341 cases of serious cardiac arrhythmias, including 80 fatalities, were reported in patients receiving cisapride. In about 85% of these cases, the adverse effects occurred in patients with known risk factors (e.g., those with conditions predisposing them to arrhythmias or those receiving concomitant drugs that may cause prolongation of the QT interval or are known to impair metabolism of cisapride).

Because of these adverse effects associated with cisapride, the professional labeling of the drug had been revised several times to inform health care professionals and patients about risks associated with the use of cisapride. In 1995, Janssen Pharmaceutica added a boxed warning to the professional labeling of the drug concerning serious cardiac arrhythmias (including death) associated with cisapride and related precautions and contraindications. Subsequently, additional cases of serious adverse effects and fatalities were reported prompting the manufacturer and the US Food and Drug Administration (FDA) to issue updated stronger warnings, precautions, and contraindications about the potential risks of cisapride, including recommendations related to performing certain diagnostic tests (e.g., ECG evaluation, blood tests) prior to initiation of therapy with the GI motility stimulant.

In January 2000, FDA announced that a public advisory committee meeting would be held in April, 2000 where safety of cisapride and additional methods to reduce development of adverse effects would be discussed. However, despite these risk management efforts, Janssen Pharmaceutica in consultation with FDA decided that continued prescription access in the US to cisapride would pose unacceptable risks and the drug was withdrawn from the US market in March, 2000. The public advisory committee meeting previously scheduled for April 12th was cancelled.

Clinicians should reassess the need of cisapride in each patient considering the potential risks of the drug and alternative therapies other than cisparide. Cisapride will continue to be available in the US on a restricted basis

through an investigational limited access program to patients who do not respond to all other standard treatment options or to those with severely debilitated conditions in whom the benefits of cisapride might outweigh its risks; these patients must clearly meet defined eligibility criteria.

The investigational limited access program has 3 protocols: one for adults, one for pediatric patients, and one for neonates. Under the treatment protocol, adults are eligible to receive cisapride if they have gastroesophageal reflux disease (GERD), gastroparesis, pseudo-obstruction, or severe constipation. Pediatric patients are eligible to receive cisapride if they have refractory GERD (associated with failure to thrive, asthma, bradycardia, apnea, or other severe condition) or pseudo-obstruction. Neonates are eligible to receive cisapride if they have feeding intolerance. In addition, to be eligible for enrollment in the investigational limited access program, patients must undergo an appropriate diagnostic evaluation, including radiologic examinations or endoscopy. Patients also must undergo baseline screening tests, including laboratory tests and ECG to rule out risk factors that are contraindicated in patients receiving cisapride, and evaluation by a clinician, laboratory tests, and ECG must be repeated at regular intervals while patients are enrolled in the program. Physicians participating in the limited access program must be board eligible or certified in one or more medical specialties (i.e., internal medicine [including gastroenterology and cardiology], family practice, pediatrics [including neonatology], surgery). If the participating physician is not a gastroenterologist, the patient also must be under the care of a gastroenterologist by consultation. Since the protocols reflect investigational use of cisapride, institutional review board approval, completion of an FDA form 1572, and signed informed consent also are required. Enrollment in the investigational limited access program started in May 1st, 2000. Physicians interested in enrolling patients or obtaining further information regarding the investigational limited access program should contact the manufacturer at 877-795-4247.

All serious adverse effects associated with use of cisapride must be reported to Janssen Pharmaceutica at 800-JANSSEN (800-526-7736) or to the FDA MedWatch Program by phone (800-FDA-1088), by fax (800-FDA-0178), by the internet ([Web]), or by mail (MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787).

For additional medical information concerning use of cisapride, the manufacturer may be contacted at 800-JANSSEN (800-526-7736) from 9 a.m.–5 p.m. ET, M–F.

Introduction

Cisapride is a stimulant of GI motility (prokinetic agent).

Uses for Cisapride

Gastroesophageal Reflux

Cisapride is used for the symptomatic (e.g., nocturnal heartburn) relief of gastroesophageal reflux. Drug therapy (e.g., antacids, alginic acid, prokinetic agents, histamine H_2-receptor antagonists, proton-pump inhibitors) for gastroesophageal reflux is used in adults who are unresponsive to conventional nondrug therapy alone, including changes in lifestyle, habits, and/or diet that may be contributing factors, and weight reduction in obese patients. Suppression of gastric acid secretion is considered by the American College of Gastroenterology (ACG) to be the mainstay of treatment for gastroesophageal reflux disease (GERD), and a proton-pump inhibitor or histamine H_2-receptor antagonist is used to achieve acid suppression, control symptoms, and prevent complications of the disease.

Because of the risk of serious, sometimes fatal ventricular arrhythmias, therapy with cisapride generally has been reserved for patients who do not respond adequately to lifestyle modifications, antacids, and gastric acid reducing agents. (See Cautions.)

Contributing factors for the development of increased reflux of gastric contents into the esophagus and GERD include increased gastric volume aggravated by delayed gastric emptying, decreased resting lower esophageal sphincter pressure relative to intragastric pressure, and decreased esophageal clearance. Patients with gastroesophageal reflux may experience reflux episodes throughout the day and night, and heartburn, the principal symptom of reflux, is more severe in the supine position. In addition, because peristalsis, swallowing, fluid intake, and saliva production are reduced or absent during sleep, the magnitude of reflux and period of exposure of the esophagus to gastric acid and enzymes may be most pronounced at this time (resulting in nocturnal heartburn and regurgitation). By increasing lower esophageal sphincter pressure, improving esophageal peristalsis, and accelerating gastric emptying, cisapride can reduce reflux and the period of esophageal exposure to low pH and other irritants and thus relieve associated symptoms (e.g., heartburn, regurgitation) in patients with gastroesophageal reflux.

In clinical studies in patients with gastroesophageal reflux and in healthy individuals, cisapride increased lower esophageal sphincter pressure, esophageal motility, and acid clearance and also promoted gastric emptying; the effects of cisapride were superior to those of placebo and at least comparable to those of metoclopramide. However, in several placebo-controlled clinical trials in patients with symptomatic gastroesophageal reflux in which most patients had normal pretreatment and posttreatment lower esophageal pressures, oral cisapride dosages of 10 or 20 mg 4 times daily reduced nocturnal heartburn but produced no appreciable effect on lower esophageal sphincter pressure nor any consistent effect on daytime heartburn, regurgitation, or esophageal histopathology. In addition, oral administration of cisapride may increase lower esophageal sphincter pressure less consistently than IV administration of the drug. In patients with symptomatic gastroesophageal reflux and in healthy individuals, lower esophageal sphincter pressure was increased after administration of single, IV cisapride doses of 4–10 mg or after multiple oral doses of 10 mg 3 times daily; lower esophageal sphincter pressure also was increased in healthy individuals after a single oral 20-mg dose, but lower single oral doses were not effective. In addition to symptomatic relief, short-term endoscopic evidence of healing has been reported in about 55–90% of patients with reflux esophagitis receiving cisapride dosages of 10 mg 4 times daily for 6–16 weeks; antacid requirements also have decreased during cisapride therapy. While the drug has been more effective than placebo in promoting healing in several studies, there is some evidence that relatively high dosages (e.g., 20 mg 4 times daily) may be needed for substantial improvement in healing rates with cisapride relative to placebo.

Cisapride appears to be comparably effective to H_2-receptor antagonists (e.g., cimetidine, ranitidine), and combined therapy with the drugs appears to be more effective in providing symptomatic relief and promoting healing than H_2-antagonists alone. However, proton-pump inhibitors are more effective than cisapride in controlling gastric acid reflux and relieving GERD symptoms without the risk of severe adverse cardiac effects associated with cisapride. In a controlled study comparing 5 different maintenance therapies for GERD, remission of GERD symptoms was maintained after 12 months of therapy in 80% of patients receiving omeprazole alone versus 54% of those receiving cisapride alone and 66% in those receiving cisapride in combination with ranitidine.

Cisapride Dosage and Administration

Administration

Cisapride is administered orally. Cisapride should be administered orally on an empty stomach at least 15 minutes before meals in order to maintain relatively consistent GI absorption.

Concomitant oral administration of cisapride and grapefruit juice should be avoided because grapefruit juice may increase the risk of QT interval prolongation. (See Cautions: Precautions and Contraindications.)

A 12-lead ECG should be performed prior to initiation of cisapride therapy, and the drug should not be administered to patients who have QT_c intervals exceeding 450 milliseconds. Determination of serum electrolytes (potassium, calcium, and magnesium) and serum creatinine also should be performed prior to initiation of cisapride therapy and whenever

conditions develop that may affect electrolyte balance or renal function.

Dosage

Dosage of cisapride monohydrate is expressed in terms of anhydrous cisapride and should be individualized according to patient response and tolerance. The recommended dosage of cisapride should not be exceeded.

For the management of gastroesophageal reflux in adults, cisapride therapy is initiated with an oral dosage of 10 mg 4 times daily, at least 15 minutes before meals and at bedtime; the bedtime dose can reduce the potential for reflux during sleep and associated symptoms (e.g., nocturnal heartburn. Occasionally, it may be necessary to increase the dosage to 20 mg 4 times daily to achieve a satisfactory response. Cisapride therapy should be discontinued if relief of nocturnal heartburn does not occur. The minimum effective dosage of the drug should be used; the recommended dosage of cisapride should not be exceeded.

While a prolongation in the elimination half-life of cisapride resulting in increased steady-state plasma concentrations has been observed in geriatric patients, the manufacturer states that therapeutic dosages for geriatric patients are similar to those used in younger adults.

The manufacturer states that safety and efficacy of cisapride in children younger than 16 years of age have not been established.

Dosage in Renal and Hepatic Impairment

The manufacturer and some clinicians state that the degree of accumulation of cisapride and/or its metabolites may be somewhat higher in patients with hepatic and/or renal impairment when compared with healthy adults, although the manufacturer states that such differences in accumulation are not consistent. However, the manufacturer and some clinicians recommend that patients with hepatic insufficiency be treated initially with half the usual dosage of cisapride. Since some evidence suggests that the risk of QT prolongation and associated serious cardiac arrhythmias, including torsades de pointes, is increased in patients with conditions that affect the metabolism and result in increased serum concentrations of cisapride, some clinicians state that the drug should be used with caution in patients with renal insufficiency; the manufacturer states that the drug is contraindicated in patients with renal failure. (See Cautions: Precautions and Contraindications.)

Detailed Cisapride dosage information

Cautions for Cisapride

Numerous cases of serious cardiac arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsades de pointes, QT-interval prolongation) have been reported in patients taking cisapride; fatalities have been reported. Many of these patients were receiving drugs expected to increase serum cisapride concentrations by inhibiting the cytochrome P-450 enzymes that metabolize cisapride (CYP3A4) or had other predisposing factors to arrhythmia development (e.g., history of QT prolongation or ventricular arrhythmias, concomitant drug therapy associated with QT-interval prolongation). (See Cautions: Cardiovascular Effects and see Cautions: Precautions and Contraindications.) QT prolongation, transient ventricular tachycardia (e.g., torsades de pointes), syncope, cardiac arrest, and/or sudden death also have been reported with high-dose cisapride therapy (i.e., 40 mg every 6 hours) and infrequently in patients without identifiable risk factors. Because of the risk of serious, sometimes fatal ventricular arrhythmias, therapy with cisapride generally should be reserved for patients who do not respond adequately to lifestyle modifications, antacids, and gastric acid reducing agents. The recommended dosage of cisapride (10–20 mg 4 times daily) should *not* be exceeded.

Adverse effects on the GI tract and nervous system are the most frequently reported adverse effects of cisapride and

those most frequently requiring discontinuance of the drug (usually because of intolerable diarrhea and/or abdominal pain). The most common adverse GI effects (e.g., diarrhea) are extensions of the drug's pharmacologic activity. Because of differences in the pharmacologic profiles of the drugs, adverse nervous system effects are less common with cisapride than with metoclopramide whereas diarrhea is more common with cisapride.

In adults receiving cisapride for motility disorders in US placebo-controlled clinical trials, including those with gastroesophageal reflux disease, the most frequent adverse effects of cisapride were headache, diarrhea, abdominal pain, nausea, constipation, and rhinitis. The frequency of diarrhea, abdominal pain, constipation, flatulence, and rhinitis appears to be dose dependent, occurring more frequently in patients receiving oral cisapride 20 mg 4 times daily than in those receiving 10 mg 4 times daily. Many adverse effects reported with cisapride occurred at a frequency similar to that associated with placebo, and a causal relationship to the drug often could not be established.

Cardiovascular Effects

Numerous cases of serious cardiac arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsades de pointes, QT-interval prolongation) have been reported in patients taking cisapride; fatalities have been reported. Many of the patients experiencing these arrhythmias were receiving concomitant therapy with drugs expected to increase plasma cisapride concentrations through inhibition of the cytochrome P-450 (CYP) 3A4 isoenzyme that metabolizes cisapride, including (but not limited to) certain macrolide antibiotics (clarithromycin, erythromycin, troleandomycin), certain antifungal agents (fluconazole, itraconazole, ketoconazole), certain protease inhibitors (indinavir, ritonavir), and certain antidepressants (nefazodone). Other such patients had disorders predisposing them to arrhythmias with cisapride therapy, including preexisting heart disease and/or a history of arrhythmia, renal failure, or electrolyte imbalance, or were receiving concomitant therapy with other drugs associated with arrhythmia or QT prolongation. (See Cautions: Precautions and Contraindications.)

Current data suggest that concomitant administration of cisapride and certain azole-derivative antifungal agents (e.g., fluconazole, itraconazole, ketoconazole) can result in prolongation of the QT interval. Cisapride is metabolized by the CYP3A4 isoenzyme. Pharmacokinetics studies in humans demonstrate that oral ketoconazole markedly inhibits the metabolism of cisapride, resulting in an average eightfold increase in AUC of cisapride. A study in healthy men and women suggests that concomitant administration of cisapride and ketoconazole can produce prolongation of the QT interval. In vitro data suggest that itraconazole, miconazole (systemic form no longer commercially available in the US), nefazodone, indinavir, ritonavir, clarithromycin, erythromycin, and troleandomycin also markedly inhibit the biotransformation system mainly responsible for the metabolism of cisapride. In addition, several studies indicate that concomitant administration of grapefruit juice and cisapride increases the mean bioavailability of the drug by 50%. (See Cautions: Precautions and Contraindications.) Therefore, the manufacturer of cisapride states that concomitant administration of cisapride and oral ketoconazole, itraconazole, oral or IV fluconazole, nefazodone, oral or IV erythromycin, clarithromycin, troleandomycin, indinavir, ritonavir, or grapefruit juice is contraindicated. The possibility that other inhibitors of the CYP3A4 isoenzyme also may interact with cisapride should be considered, and the manufacturers of nelfinavir and saquinavir state that these drugs should not be used concomitantly with cisapride.

Because cisapride is a type 4 serotonin (5-HT_4) receptor agonist, exhibiting partial agonist activity at these receptors in cardiac tissue, the drug may exhibit positive chronotropic activity. However, palpitation, which may be accompanied by chest and arm pain, occurred in 1% or less of patients receiving cisapride in controlled clinical trials.

Tachycardia and extrasystoles have been reported in patients receiving cisapride in US and foreign trials and in foreign marketing experience. Rare occurrences of sinus tachycardia, with relapse of such tachycardia after drug rechallenge in some cases also have been reported.

Hypertension also has been reported with cisapride therapy.

Nervous System Effects

Headache was the most frequent adverse nervous system effect of cisapride in placebo-controlled clinical trials, occurring in about 19% of patients (17% of those receiving placebo) and causing discontinuance of the drug in about 1%. Pain occurred in about 3% of patients receiving cisapride (2% of those receiving placebo). Insomnia occurred in about 2%, anxiety in 1.4%, and nervousness in 1.4% of patients receiving cisapride (0.7–1.3% of those receiving placebo), and discontinuance of the drug was required in 0.3, 0.1, and 0.2% of patients, respectively. Dizziness, myalgia, fatigue, and depression were reported in more than 1% of patients in controlled clinical trials. Somnolence, migraine, and tremor occurred in 1% or less of patients receiving cisapride in controlled clinical trials. Seizures, extrapyramidal effects, and paresthesias rarely have been reported in patients receiving cisapride in US and foreign trials and in foreign marketing experience. However, the antidopaminergic activity of cisapride in animals is less than that of metoclopramide, and therefore the risk of extrapyramidal effects is thought to be low. Psychiatric events, including confusion, depression, suicide attempt, and hallucinations, have been reported with cisapride therapy during postmarketing surveillance.

GI Effects

GI effects were among the most frequent adverse effects of cisapride reported in patients with gastroesophageal reflux or other GI motility disorders in controlled clinical trials and were those most commonly resulting in discontinuance of the drug.

Diarrhea (usually increased stool frequency) occurred in about 14% of patients receiving cisapride for gastroesophageal reflux or other GI motility disorders (10% of those receiving placebo); occasionally, cisapride-induced diarrhea may be intolerable, and has required discontinuance of the drug in 0.7% of patients in clinical trials. Abdominal pain or cramping was reported in about 10% of patients receiving cisapride (8% of those receiving placebo) . Although abdominal pain may subside within several days despite continued therapy with the drug, it was severe enough to require discontinuance of cisapride in 1.2% of patients in clinical trials. Abdominal distension and heaviness and borborygmus also have been reported. Nausea occurred in about 8% of patients receiving cisapride or placebo and required discontinuance in 1%, and constipation occurred in about 7% of patients (3% of those receiving placebo) and required discontinuance of the drug in 0.1%. Flatulence occurred in 3.5% and dyspepsia in 2.7% of patients receiving cisapride (3 and 1%, respectively, of those receiving placebo) and required discontinuance of the drug in 0.4 and 0.1%, respectively. Vomiting was reported in more than 1% of patients receiving cisapride in controlled clinical trials, and dry mouth was reported in 1% or less of patients.

Respiratory Effects

Respiratory effects were among the most frequent adverse effects of cisapride reported in patients with gastroesophageal reflux or other GI motility disorders in controlled clinical trials. Adverse respiratory effects resulted in discontinuance of the drug in 0.3% of patients.

Rhinitis was the most frequent adverse respiratory effect of cisapride, occurring in 7.3% of patients (5.7% of those receiving placebo) and requiring discontinuance in 0.1%. Sinusitis occurred in about 4% of patients, and upper respiratory tract infection occurred in about 3% of patients receiving cisapride or placebo, and may be related to underlying gastroesophageal reflux rather than the drug in some patients. Cough was reported in 1.5% of patients receiving the drug in controlled clinical trials, requiring discontinuance in 0.2% of patients, and pharyngitis was reported in more than 1% of patients. Precipitation of bronchospasm and/or deterioration in asthma control, reportedly confirmed in some cases by rechallenge and dechallenge with the drug, also has been reported in several patients with asthma receiving cisapride therapy (e.g., during postmarketing surveillance).

Genitourinary Effects

Urinary tract infection was reported in about 2% and vaginitis in about 1% of patients receiving cisapride or placebo in controlled clinical trials. Urinary frequency was reported in about 1% and required discontinuance in 0.1% of patients receiving the drug. Urinary incontinence has been reported with cisapride therapy during postmarketing surveillance.

Dermatologic and Sensitivity Reactions

Rash was reported in 1.6% and pruritus in 1.2% of patients receiving cisapride and at similar incidences in those receiving placebo in controlled clinical trials; pruritus required discontinuance of cisapride in 0.1% of patients. Edema was reported in 1% or less of patients. Allergic reactions, including bronchospasm, urticaria, and angioedema, have been reported with cisapride therapy during postmarketing surveillance.

Musculoskeletal Effects

Arthralgia occurred in 1.4% of patients receiving cisapride (1.2% of those receiving placebo) in controlled clinical trials and required discontinuance of the drug in 0.1%. Chest pain and back pain were reported in more than 1% of patients.

Ocular Effects

Abnormal vision occurred in 1.4% of patients receiving cisapride (0.3% of those receiving placebo) in controlled clinical trials and required discontinuance of the drug in 0.2% of patients.

Hepatic Effects

Although no evidence of liver function abnormalities during cisapride therapy was observed in at least one large series of patients, elevated serum liver enzyme concentrations and hepatitis have been reported rarely in patients receiving the drug in US and foreign trials and in foreign marketing experience.

Hematologic Effects

Thrombocytopenia, leukopenia, aplastic anemia, pancytopenia, and granulocytopenia have been reported rarely in patients receiving cisapride in US and foreign trials and in foreign marketing experience.

Electrolyte and Metabolic Effects

Dehydration was reported in more than 1% of patients receiving cisapride in controlled clinical trials. Limited evidence indicates that cisapride does not adversely affect glycemic control in insulin-dependent (type I) diabetic patients with delayed gastric emptying.

Other Adverse Effects

Viral infection occurred in about 4% of patients receiving cisapride in controlled clinical trials and required discontinuance of the drug in 0.2% of patients. Fever was reported in about 2% of patients receiving cisapride in controlled clinical trials and required discontinuance in 0.1%.

The antidopaminergic activity of cisapride in animals is less than that of metoclopramide, suggesting that cisapride may be less likely to produce hyperprolactinemic effects (e.g., galactorrhea, gynecomastia, menstrual irregularities). However, hyperprolactinemia, galactorrhea, gynecomastia, and enlargement of the female breast have been reported with cisapride therapy during postmarketing surveillance.

Precautions and Contraindications

Because of its pharmacologic effects on transit time in the stomach and small intestine, cisapride may alter the absorption of certain drugs. The extent of absorption of drugs that disintegrate, dissolve, and/or are absorbed mainly in the stomach (e.g., digoxin) may be diminished by cisapride. However, some evidence suggests that the magnitude of reductions in peak plasma digoxin concentrations and area under the plasma digoxin concentration-time curve (AUC) observed during concomitant cisapride administration are less pronounced than those observed with metoclopramide and may not be clinically important. The rate and extent of absorption of drugs that are mainly absorbed in the small intestine (e.g., acetaminophen, aspirin, diazepam, ethanol, levodopa, lithium, tetracycline) may be enhanced when administered concomitantly with cisapride. Patients receiving cisapride concomitantly with orally administered drugs that have narrow therapeutic ratios or drugs that require careful titration should be monitored closely. In addition, if plasma concentrations of orally administered concomitant drugs are being monitored, they should be reassessed when cisapride therapy is initiated and discontinued. Although cisapride does not directly affect psychomotor function or induce sedation or drowsiness when used alone, the absorption rate of benzodiazepines and alcohol may be increased by cisapride, enhancing their sedative effects. The manufacturer also cautions that coagulation time of patients receiving certain oral anticoagulants (e.g., warfarin) may increase with concomitant administration of cisapride; therefore, coagulation times should be monitored during the first few days after initiation or discontinuance of cisapride therapy in patients receiving oral anticoagulants, and appropriate adjustment in the anticoagulant dosage made if necessary. The possibility that oral bioavailability of cisapride (probably secondary to inhibited metabolism) could be increased during concomitant administration of cimetidine should be considered; ranitidine does not appear to interact with cisapride similarly. In addition, the possibility that cisapride may accelerate the GI absorption and decrease the oral bioavailability of cimetidine or ranitidine should be considered.

Because anticholinergic drugs (e.g., belladonna alkaloids, dicyclomine) may decrease GI motility, concomitant administration of these drugs may compromise the beneficial therapeutic effects of cisapride.

Some clinicians suggest that cisapride should be used with caution in patients who have a history of asthma, since bronchospasm and/or deterioration in asthma control has been reported rarely in such patients. (See Cautions: Respiratory Effects.)

Patients should be advised that lifestyle changes, including avoidance of alcohol, cessation or reduction of cigarette smoking, elevation of the head of the bed, avoidance of large meals just before bedtime, weight loss, and avoidance of fatty foods, chocolate, caffeine, and citrus, generally should be tried before using any drug, including cisapride, for nighttime heartburn. Patients should be advised to seek medical attention if they faint or become faint, dizzy, experience an irregular heartbeat or pulse, or any other unusual symptoms while using cisapride. Patients should be questioned about their use of other medications and should be advised to inform their clinician when new medications are added to their regimen.

Potential benefits should be weighed against risks prior to administration of cisapride to patients who have conditions, such as multiple organ failure, chronic obstructive pulmonary disease (COPD), apnea, and advanced cancer, that could predispose them to the development of serious arrhythmias.

A 12-lead ECG should be obtained prior to initiation of cisapride therapy, and the drug should not be administered if the QT_C interval exceeds 450 milliseconds. Serum electrolytes (potassium, calcium, and magnesium) and serum creatinine also should be assessed prior to administration of cisapride and whenever conditions develop that may affect electrolyte balance or renal function. Patients should be instructed to immediately stop taking cisapride and contact a physician if they experience syncope or rapid or irregular heartbeat.

Cisapride is contraindicated in patients with conditions predisposing them to arrhythmias, including a history of prolonged QT intervals on ECG or known family history of congenital long QT syndrome; a history of ventricular arrhythmias (e.g., torsades de pointes), ischemic or valvular heart disease; other structural heart defects; cardiomyopathy; congestive heart failure; clinically important bradycardia; sinus node dysfunction; second- or third-degree atrioventricular (AV) block;

respiratory failure; or conditions that result in electrolyte disorders, such as severe dehydration, vomiting, malnutrition, eating disorders, renal failure, or during administration of potassium-wasting diuretics or insulin in acute settings.

Cisapride is contraindicated in patients receiving concomitant therapy with drugs known to prolong the QT interval and increase the risk of arrhythmias, including (but not limited to) antiarrhythmics of class 1A (e.g., quinidine, procainamide) and class III (e.g., sotalol), tricyclic antidepressants (e.g., amitriptyline, protriptyline), certain tetracyclic or other antidepressants (e.g., maprotiline, nefazodone), certain antipsychotic agents (e.g., sertindole [not currently commercially available in the US]), certain phenothiazines (e.g., prochlorperazine, promethazine), astemizole (no longer commercially available in the US), bepridil, sparfloxacin, and terodiline (not currently commercially available in the US). Cisapride also is contraindicated in patients receiving concomitant therapy with drugs expected to increase plasma cisapride concentrations through inhibition of the cytochrome P-450 (CYP) 3A4 isoenzyme that metabolizes cisapride, including (but not limited to) clarithromycin, erythromycin, troleandomycin, nefazodone, fluconazole, itraconazole, ketoconazole, indinavir, ritonavir and aprepitant or fosaprepitant. (See Cautions: Cardiovascular Effects.)

Concomitant oral administration of grapefruit juice has been reported to increase the bioavailability and blood levels of cisapride. This interaction appears to result from inhibition of the intestinal cytochrome P-450 enzyme system. Clinicians should advise patients to refrain from ingesting grapefruit juice during cispride therapy due to the potential for prolongation of the QT interval.

Cisapride is contraindicated in patients in whom an increase in GI motility could be harmful (e.g., patients with GI perforation, hemorrhage, or mechanical obstruction). Cisapride also is contraindicated in patients with known sensitivity or intolerance to the drug.

Pediatric Precautions

Safety and efficacy of cisapride in children younger than 16 years of age have not been established for any indication. However, limited data in children 2 months of age and older who have received the drug (e.g., for gastroesophageal reflux), suggest that the adverse effect profile is similar to that in adults. Although a causal relationship to cisapride has not been established, serious adverse events, including death, have been reported in infants and children treated with cisapride. Several deaths in pediatric patients were related to cardiovascular events (third-degree heart block and ventricular tachycardia). Pediatric deaths also have been associated with seizures, and at least one case of sudden unexplained death has been reported in a 3-month-old infant. Other adverse effects reported specifically in pediatric patients include positive antinuclear antibody (ANA) test results, 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.

Geriatric Precautions

Cisapride generally is well tolerated in geriatric patients; the frequency and severity of adverse effects reported in patients older than 65 years of age are similar to those in younger adults. However, caution in the use of cisapride must be exercised in geriatric patients since a substantial proportion of such patients have conditions or use concomitant drugs that contraindicate therapy with cisapride. (See Cautions: Precautions and Contraindications.) A 12-lead ECG and serum electrolyte determinations should be performed prior to initiation of cisapride in geriatric patients. Steady-state plasma concentrations of cisapride generally may be higher in geriatric patients than in younger adults secondary to a moderate prolongation of half-life; however, the manufacturer states that therapeutic dosages for geriatric patients are similar to those for younger adults.

Mutagenicity and Carcinogenicity

No evidence of mutagenicity was demonstrated by cisapride in the in vitro Ames test, the human lymphocyte

chromosomal aberration test, the rat hepatocyte UDS test, the in vivo rat micronucleus test, the mouse lymphoma cell forward mutation test, the dominant lethal mutation test in male and female mice, or the sex-linked recessive lethal test in *Drosophila melanogaster*.

Studies to determine the carcinogenic potential of cisapride were performed in mice and rats; cisapride was not tumorigenic in these studies. Mice received cisapride orally in dosages of up to 80 mg/kg daily for 76 weeks, while rats received this dosage for 100 weeks. The maximum dosages used in mice and rats were equal to or less than 4 and 7 times the maximum recommended human dosage on a body surface area basis, respectively, and were equal to or less than 50 times the maximum recommended human dosage on a mg/kg basis.

Pregnancy, Fertility, and Lactation

Pregnancy

Reproduction studies in rats and rabbits receiving cisapride dosages of up to 100 and 24 times, respectively, the human daily dosage of the drug on a mg/kg basis, did not reveal evidence of teratogenicity; however, cisapride has been shown to be embryotoxic and fetotoxic in rats and rabbits when given at dosages equal to or more than 100 and 12 times, respectively, the maximum recommended dosage in humans on a mg/kg basis. Cisapride given to female rats at daily dosages 25 and 100 times the maximum recommended dosage in humans has been shown to decrease birth weights and adversely affect the survival rate of rat pups. Although there are no adequate and controlled studies to date in humans, cisapride should be used during pregnancy only when the potential benefits justify the possible risks to the fetus.

Fertility

Reproduction studies in male rats receiving cisapride doses of up to 100 times the human daily dose of the drug on a mg/kg basis did not reveal any evidence of an effect on fertility or reproductive performance; however, cisapride has been shown to prolong the breeding interval required for impregnation in female rats and in the offspring of female rats given daily dosages equal to or more than 25 and 6.25 times, respectively, the maximum recommended dosage in humans on a mg/kg basis. Cisapride also has been shown to exert contragestational or pregnancy-disrupting effects in female rats when given at dosages equal to 100 times the human daily dose of the drug on a mg/kg basis.

Lactation

Cisapride is distributed into human milk at concentrations about 5% of those found in plasma. Since the potential effect on nursing infants is not known, cisapride should be used with caution in nursing women.

Description

Cisapride, a synthetic substituted piperidinyl benzamide, is a stimulant of GI motility (prokinetic agent). Cisapride is commercially available as the monohydrate; potency is expressed in terms of anhydrous drug.

Cisapride is structurally related to metoclopramide. Like metoclopramide, the drug is a substituted benzamide derivative of *p*-aminobenzoic acid and is structurally related to procainamide, but lacks local anesthetic and antiarrhythmic properties. Cisapride differs structurally from metoclopramide by replacement of the 2-diethylaminoethyl substituent at the *p*-aminobenzamide nitrogen with a substituted piperidinyl substituent. While both drugs stimulate gastric and small intestinal motility, the pharmacologic profile of metoclopramide is more complex than that of cisapride. Cisapride appears to stimulate GI motility principally via enhancement of cholinergic excitatory processes at the postganglionic neuromuscular junction (i.e., stimulating acetylcholine release from postganglionic neurons of the myenteric [Auerbach's] plexus); this effect appears to be indirect, and it has been suggested that serotonergic (e.g., type 4 [5-HT_4]) receptor agonist activity may be involved in the release of the neurotransmitter. While metoclopramide also exhibits such activity at postganglionic neurons, cisapride, unlike metoclopramide, does not exhibit potent dopamine-receptor antagonist activity

nor does it appear to possess direct antiemetic or CNS depressant (e.g., sedative) activity. The antidopaminergic activity of cisapride has been shown to be less than that of metoclopramide in animals, and the likelihood of producing extrapyramidal or hyperprolactinemic effects (e.g., galactorrhea, gynecomastia, menstrual irregularities) with cisapride generally appears to be low.

Like metoclopramide, cisapride increases (generally by about 20–50%) lower esophageal sphincter pressure and esophageal motility in patients with gastroesophageal reflux disease and in healthy individuals. Also like metoclopramide, cisapride accelerates gastric emptying and intestinal transit from the duodenum to the ileocecal valve, and the drug's stimulatory effects on GI smooth muscle coordinate gastric, pyloric, and duodenal (i.e., antroduodenal) motor activity. However, unlike metoclopramide, cisapride also increases colonic motility and enhances cecal and ascending colonic emptying and can increase stool frequency in both healthy and constipated individuals; in part, enhanced defecation may result from decreased anal sphincter tone induced by the drug.

Electrophysiologic studies in anesthetized guinea pig and rabbit models and in isolated rabbit Purkinje fibers, ventricular papillary muscle, and ventricular myocytes have shown that cisapride prolongs cardiac repolarization without slowing conduction by selectively blocking the rapid component of the delayed rectifying potassium current (I_{kr}), which leads to a lengthening of the action potential (QT syndrome). (See Cautions.)

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Please refer to the ASHP Drug Shortages Resource Center for information on shortages of one or more of these preparations.

Cisapride

Routes	Dosage Forms	Strengths	Brand Names	Manufacturer
Oral	Suspension	5 mg (of anhydrous cisapride) per 5 mL	Propulsid	Ortho-McNeil
	Tablets	10 mg (of anhydrous cisapride)	Propulsid (scored)	Ortho-McNeil
		20 mg (of anhydrous cisapride)	Propulsid	Ortho-McNeil

Reload page with references included

More about cisapride

- Check interactions
- Compare alternatives
- Reviews (1)
- Side effects
- Dosage information

- During pregnancy
- Drug class: GI stimulants
- Breastfeeding

Professional resources

Other brands

Propulsid

Related treatment guides

- GERD
- Gastroparesis
- Indigestion

Medical Disclaimer

DRUG STATUS

Availability
Discontinued

Pregnancy & Lactation
Risk data available

CSA Schedule*
N/A Not a controlled drug

Approval History
Drug history at FDA

User Reviews & Ratings

Review this drug

Images

Propulsid (cisapride) 10 mg (JANSSEN P 10)


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