



AcipHex advertisement.

[s.l.]: [s.n.], 2000

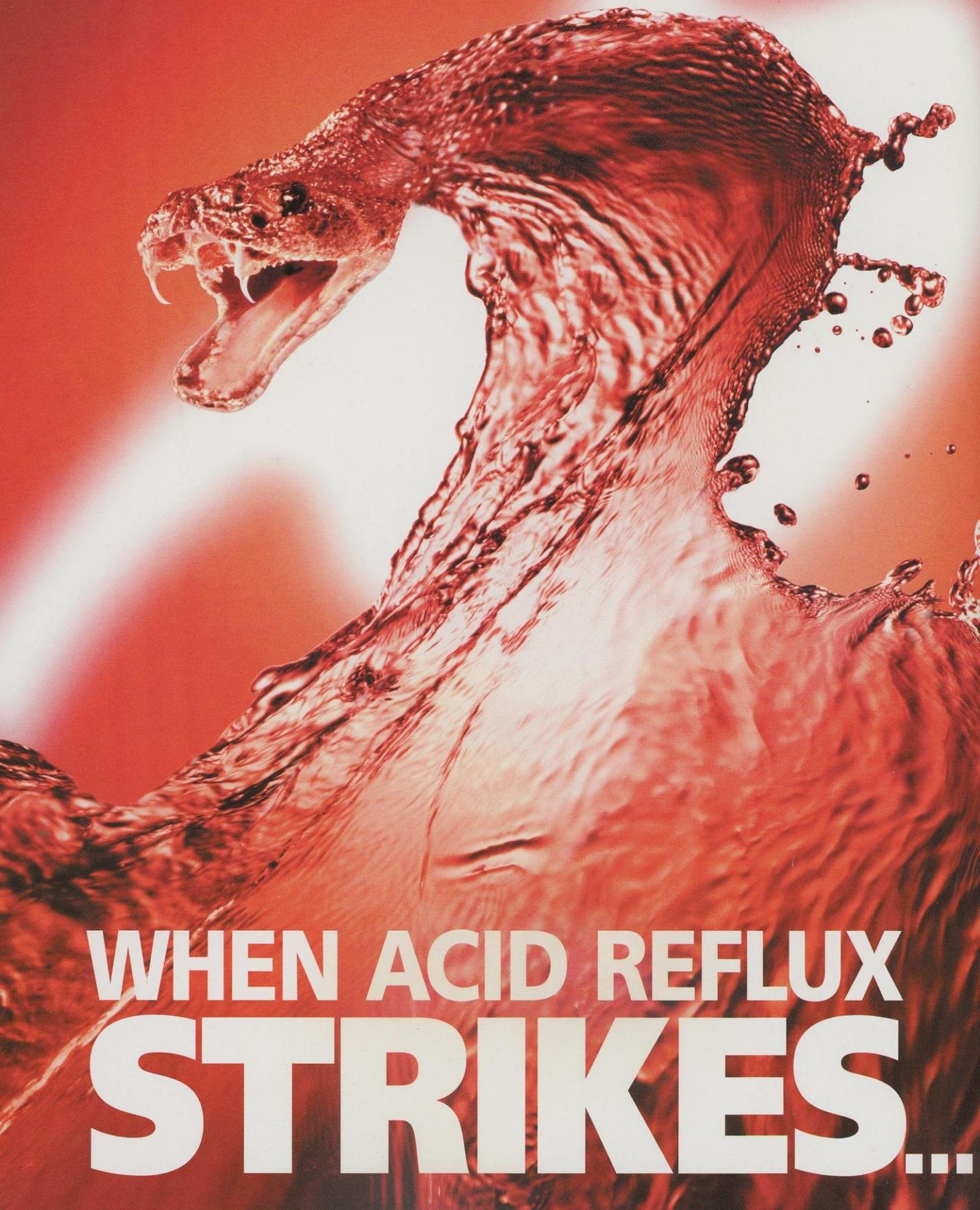
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IN ACID SUPPRESSION
FOR EROSION GERD



WHEN ACID REFLUX
STRIKES...

STRIKE



Please see brief summary of prescribing
information at the end of this advertisement.

BACK NOW WITH

ONCE-A-DAY

AcipHex® rabeprazole sodium 20-MG TABLETS

A proton pump inhibitor that offers:

Effective healing

- Significant healing and effective relief of heartburn in erosive GERD

Consistent maintenance

- Endoscopically proven maintenance of healed erosive GERD for 52 weeks
- Continued relief of major erosive GERD symptoms for 52 weeks
 - 94% to 97% of patients without relapse in daytime heartburn
 - 91% to 98% of patients without relapse in nighttime heartburn

Excellent safety profile

- The most common side effect assessed as possibly related to ACIPHEX was headache (2.4% vs 1.6% for placebo)
- Symptomatic response to therapy does not preclude the presence of gastric malignancy. ACIPHEX is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles, or to any component of the formulation

STRIKE BACK NOW

Before prescribing, please consult complete prescribing information of which the following is a brief summary.

INDICATIONS AND USAGE

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

ACIPHEX™ is indicated for short-term (4 to 8 weeks) treatment in the healing and symptomatic relief of erosive or ulcerative gastroesophageal reflux disease (GERD). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX™ may be considered.

Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

ACIPHEX™ is indicated for maintaining healing and reduction in relapse rates of heartburn symptoms in patients with erosive or ulcerative gastroesophageal reflux disease (GERD Maintenance).

Healing of Duodenal Ulcers

ACIPHEX™ is indicated for short-term (up to four weeks) treatment in the healing and symptomatic relief of duodenal ulcers. Most patients heal within four weeks.

Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome

ACIPHEX™ is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.

CONTRAINDICATIONS

Rabeprazole is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles or to any component of the formulation.

PRECAUTIONS

General

Symptomatic response to therapy with rabeprazole does not preclude the presence of gastric malignancy.

Patients with healed GERD were treated for up to 40 months with rabeprazole and monitored with serial gastric biopsies. Patients without *H. pylori* infection (221 of 326 patients) had no clinically important pathologic changes in the gastric mucosa. Patients with *H. pylori* infection at baseline (105 of 326 patients) had mild or moderate inflammation in the gastric body or mild inflammation in the gastric antrum. Patients with mild grades of infection or inflammation in the gastric body tended to change to moderate, whereas those graded moderate at baseline tended to remain stable. Patients with mild grades of infection or inflammation in the gastric antrum tended to remain stable. At baseline 8% of patients had atrophy of glands in the gastric body and 15% had atrophy in the gastric antrum. At endpoint, 15% of patients had atrophy of glands in the gastric body and 11% had atrophy in the gastric antrum. Approximately 4% of patients had intestinal metaplasia at some point during follow-up, but no consistent changes were seen.

Information for Patients

Patients should be cautioned that ACIPHEX™ delayed-release tablets should be swallowed whole. The tablets should not be chewed, crushed, or split.

Drug Interactions

Rabeprazole is metabolized by the cytochrome P450 (CYP450) drug metabolizing enzyme system. Studies in healthy subjects have shown that rabeprazole does not have clinically significant interactions with other drugs metabolized by the CYP450 system, such as warfarin and theophylline given as single oral doses, diazepam as a single intravenous dose, and phenytoin given as a single intravenous dose (with supplemental oral dosing). *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporine metabolism with an IC_{50} of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days of dosing with 20 mg of rabeprazole. This degree of inhibition is similar to that by omeprazole at equivalent concentrations.

Rabeprazole produces sustained inhibition of gastric acid secretion. An interaction with compounds which are dependent on gastric pH for absorption may occur due to the magnitude of acid suppression observed with rabeprazole. For example, in normal subjects, coadministration of rabeprazole 20 mg QD resulted in an approximately 30% decrease in the bioavailability of ketoconazole and increases in the AUC and C_{max} for digoxin of 19% and 29%, respectively. Therefore, patients may need to be monitored when such drugs are taken concomitantly with rabeprazole. Co-administration of rabeprazole and antacids produced no clinically relevant changes in plasma rabeprazole concentrations.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 88/104-week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumor occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 $\mu\text{g}\cdot\text{hr}/\text{mL}$ which is 1.6 times the human exposure (plasma AUC_{0-24} = 0.88 $\mu\text{g}\cdot\text{hr}/\text{mL}$) at the recommended dose for GERD (20 mg/day). In a 104-week carcinogenicity study in Sprague-Dawley rats, males were treated with oral doses of 5, 15, 30, and 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumors in female rats at all doses including the lowest tested dose. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 $\mu\text{g}\cdot\text{hr}/\text{mL}$, which is about 0.1 times the human exposure at the recommended dose for GERD. In male rats, no treatment related tumors were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 $\mu\text{g}\cdot\text{hr}/\text{mL}$ (0.2 times the human exposure at the recommended dose for GERD).

Rabeprazole was positive in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward gene mutation test and the mouse lymphoma cell (L5178Y/TK-/-) forward gene mutation test. Its demethylated-metabolite was also positive in the Ames test. Rabeprazole was negative in the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test, and the *in vivo* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 $\mu\text{g}\cdot\text{hr}/\text{mL}$, about 10 times the human exposure at the recommended dose for GERD) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy

Teratogenic Effects. Pregnancy Category B: Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 $\mu\text{g}\cdot\text{hr}/\text{mL}$, about 13 times the human exposure at the recommended dose for GERD) and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 $\mu\text{g}\cdot\text{hr}/\text{mL}$, about 8 times the human exposure at the recommended dose for GERD) and have revealed no evidence of impaired fertility or harm to the fetus due to rabeprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Following intravenous administration of ¹⁴C-labeled rabeprazole to lactating rats, radioactivity in milk reached levels that were 2- to 7-fold higher than levels in the blood. It is not known if unmetabolized rabeprazole is excreted in human breast milk. Administration of rabeprazole to rats in late gestation and during lactation at doses of 400 mg/kg/day (about 195-times the human dose based on mg/m²) resulted in decreases in body weight gain of the pups. Since many drugs are excreted in milk, and because of the potential for adverse reactions to nursing infants from rabeprazole, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and efficacy of rabeprazole in pediatric patients has not been established.

Use in Women

Duodenal ulcer and erosive esophagitis healing rates in women are similar to those in men. Adverse events and laboratory test abnormalities in women occurred at rates similar to those in men.

Geriatric Use

Of the total number of subjects in clinical studies of ACIPHEX™, 19% were 65 years and over, while 4% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Worldwide, over 2900 patients have been treated with rabeprazole in Phase II-III clinical trials involving various dosages and durations of treatment. In general, rabeprazole treatment has been well-tolerated in both short-term and long-term trials. The adverse events rates were generally similar between the 10 and 20 mg doses.

Incidence in Controlled North American and European Clinical Trials

In an analysis of adverse events assessed as possibly or probably related to treatment appearing in greater than 1% of ACIPHEX™ patients and appearing with greater frequency than placebo in controlled North American and European trials, the incidence of headache was 2.4% (n=1552) for ACIPHEX™ versus 1.6% (n=258) for placebo.

In short and long-term studies, the following adverse events, regardless of causality, were reported in ACIPHEX™-treated patients. Rare events are those reported in $\leq 1/1000$ patients.

Body as a Whole: asthenia, fever, allergic reaction, chills, malaise, chest pain substernal, neck rigidity, photosensitivity reaction. **Respiratory:** abdomen enlarged, face edema, hangover effect. **Cardiovascular System:** hypertension, myocardial infarct, electrocardiogram abnormal, migraine, syncope, angina pectoris, bundle branch block, palpitation, sinus bradycardia, tachycardia. **Rare:** bradycardia, pulmonary embolus, supraventricular tachycardia, thrombophlebitis, vasodilation, OTC prolongation and ventricular tachycardia. **Digestive System:** diarrhea, nausea, abdominal pain, vomiting, dyspepsia, flatulence, constipation, dry mouth, eructation, gastroenteritis, rectal hemorrhage, melena, anorexia, cholelithiasis, mouth ulceration, stomatitis, dysphagia, gingivitis, cholelithiasis, increased appetite, abnormal stools, colitis, esophagitis, glossitis, pancreatitis, proctitis. **Rare:** bloody diarrhea, cholangitis, duodenitis, gastrointestinal hemorrhage, hepatic encephalopathy, hepatitis, hepatoma, liver fatty deposit, salivary gland enlargement, thirst. **Endocrine System:** hyperthyroidism, hypothyroidism. **Hemic & Lymphatic System:** anemia, ecchymosis, lymphadenopathy, hypochromic anemia. **Metabolic & Nutritional Disorders:** peripheral edema, edema, weight gain, gout, dehydration, weight loss. **Musculo-Skeletal System:** myalgia, arthritis, leg cramps, bone pain, arthrosis, bursitis. **Rare:** twitching. **Nervous System:** insomnia, anxiety, dizziness, depression, nervousness, somnolence, hypertension, neuropathy, vertigo, convulsion, abdominal dreams, libido decreased, neuropathy, paresthesia, tremor. **Rare:** agitation, amnesia, confusion, extrapyramidal syndrome, hyperkinesia. **Respiratory System:** dyspnea, asthama, epistaxis, laryngitis, hiccup, hyperventilation. **Rare:** apnea, hypoventilation. **Skin and Appendages:** rash, pruritis, sweating, urticaria, alopecia. **Rare:** dry skin, herpes zoster, psoriasis, skin discoloration. **Special Senses:** cataract, amblyopia, glaucoma, dry eyes, abnormal vision, tinnitus, otitis media. **Rare:** corneal opacity, blurry vision, diplopia, deafness, eye pain, retinal degeneration, strabismus. **Urogenital System:** cystitis, urinary frequency, dysmenorrhea, dysuria, kidney calculus, metrorrhagia, polyuria. **Rare:** breast enlargement, hematuria, impotence, leukorrhea, menorrhagia, orchitis, urinary incontinence.

Laboratory Values: The following changes in laboratory parameters were reported as adverse events: abnormal platelets, albuminuria, creatine phosphokinase increased, erythrocytes abnormal, hypercholesterolemia, hyperglycemia, hyperlipemia, hypokalemia, hypotension, leukocytosis, leukorrhea, liver function tests abnormal, prostatic specific antigen increase, SGPT increased, urine abnormality, WBC abnormal.

In controlled clinical studies, 3/1456 (0.2%) patients treated with rabeprazole and 2/237 (0.8%) patients treated with placebo developed treatment-emergent abnormalities (which were either new on study or present at study entry with an increase of 1.25 times baseline value) in SGOT (AST), SGPT (ALT), or both. None of the three rabeprazole patients experienced chills, fever, right upper quadrant pain, nausea or jaundice.

Post-Marketing Adverse Events: Additional adverse events reported from worldwide marketing experience with rabeprazole sodium are: sudden death, coma and hyperammonemia, jaundice, rhabdomyolysis, disorientation and delirium, bullous and other drug eruptions of the skin, interstitial pneumonia, and TSH elevations. In most instances, the relationship to rabeprazole sodium was unclear. In addition, agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, and thrombocytopenia have been reported.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug. There has been no experience with large overdoses with rabeprazole. Seven reports of accidental overdose with rabeprazole have been received. The maximum reported overdose was 80 mg. There were no clinical signs or symptoms associated with any reported overdose. Patients with Zollinger-Ellison syndrome have been treated with up to 120 mg rabeprazole QD. No specific antidote for rabeprazole is known. Rabeprazole is extensively protein bound and is not readily dialyzable. In the event of overdose, treatment should be symptomatic and supportive.

Single oral doses of rabeprazole at 786 mg/kg and 1024 mg/kg were lethal to mice and rats, respectively. The single oral dose of 2000 mg/kg was not lethal to dogs. The major symptoms of acute toxicity were hypoadipathy, labored respiration, lateral or prone position and convulsion in mice and rats and watery diarrhea, tremor, convolution and coma in dogs.

DOSAGE AND ADMINISTRATION

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

The recommended adult oral dose is one ACIPHEX™ 20 mg delayed-release tablet to be taken once daily for four to eight weeks. (See INDICATIONS AND USAGE). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX™ may be considered.

Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD Maintenance)

The recommended adult oral dose is one ACIPHEX™ 20 mg delayed-release tablet to be taken once daily. (See INDICATIONS AND USAGE).

Healing of Duodenal Ulcers

The recommended adult oral dose is one ACIPHEX™ 20 mg delayed-release tablet to be taken once daily after the morning meal for a period up to four weeks. (See INDICATIONS AND USAGE). Most patients with duodenal ulcer heal within four weeks. A few patients may require additional therapy to achieve healing.

Treatment of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

The dosage of ACIPHEX™ in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Some patients may require divided doses. Doses up to 100 mg QD and 60 mg BID have been administered. Some patients with Zollinger-Ellison syndrome have been treated continuously with ACIPHEX™ for up to one year.

No dosage adjustment is necessary in elderly patients, in patients with renal disease or in patients with mild to moderate hepatic impairment. Administration of rabeprazole to patients with mild to moderate liver impairment resulted in increased exposure and decreased elimination. Due to the lack of clinical data on rabeprazole in patients with severe hepatic impairment, caution should be exercised in those patients.

ACIPHEX™ tablets should be swallowed whole. The tablets should not be chewed, crushed, or split.

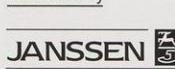


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Made in Japan

Marketed by



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• PHARMACEUTICA •
RESEARCH FOUNDATION •

Teaneck, NJ 07666

Titusville, NJ 08560-0200

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May 2000

Printed in USA

IN ACID SUPPRESSION FOR EROSIONAL GERD

STRIKE BACK NOW

**DAY
OR
NIGHT**

WITH

ONCE-A-DAY

AcipHex®
rabeprazole sodium

20-MG TABLETS

A proton pump inhibitor with:

- Potent 24-hour acid control with the first dose¹
- Significant symptom relief day or night²
- An excellent safety profile

The most common side effect assessed as possibly related to ACIPHEX was headache (2.4% vs 1.6% for placebo).

Symptomatic response to therapy does not preclude the presence of gastric malignancy. ACIPHEX is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles, or to any component of the formulation.

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INDICATIONS AND USAGE

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PRECAUTIONS

General

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Information for Patients

Patients should be cautioned that ACIPHEX® delayed-release tablets should be swallowed whole. The tablets should not be chewed, crushed, or split.

Drug Interactions

Rabeprazole is metabolized by the cytochrome P450 (CYP450) drug metabolizing enzyme system. Studies in healthy subjects have shown that rabeprazole does not have clinically significant interactions with other drugs metabolized by the CYP450 system, such as warfarin and theophylline given as single oral doses, diazepam as a single intravenous dose, and phenytoin given as a single intravenous dose (with supplemental oral dosing). *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporine metabolism with an IC_{50} of 62 micromolar a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days of dosing with 20 mg of rabeprazole. This degree of inhibition is similar to that by omeprazole at equivalent concentrations.

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Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 88/104-week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumor occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 $\mu\text{g}\cdot\text{hr}/\text{mL}$ which is 1.6 times the human exposure (plasma AUC_{0-24} = 0.88 $\mu\text{g}\cdot\text{hr}/\text{mL}$) at the recommended dose for GERD (20 mg/day). In a 104-week carcinogenicity study in Sprague-Dawley rats, males were treated with oral doses of 5, 15, 30 and 60 mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoma tumors in female rats at all doses including the lowest tested dose. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 $\mu\text{g}\cdot\text{hr}/\text{mL}$ which is about 0.1 times the human exposure at the recommended dose for GERD. In male rats, no related tumors were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 $\mu\text{g}\cdot\text{hr}/\text{mL}$ (0.2 times the human exposure at the recommended dose for GERD).

Rabeprazole was positive in the Ames test, the Chinese hamster ovary cell (CHO)/HGPRT forward gene mutation test and the mouse lymphoma cell (L5178Y/TK+/−) forward gene mutation test. Its demethylated-metabolite was also positive in the Ames test. Rabeprazole was negative in the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test, and the *in vivo* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

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Teratogenic Effects. Pregnancy Category B: Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 $\mu\text{g}\cdot\text{hr}/\text{mL}$, about 13 times the human exposure at the recommended dose for GERD) and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 $\mu\text{g}\cdot\text{hr}/\text{mL}$, about 8 times the human exposure at the recommended dose for GERD) and have revealed no evidence of impaired fertility or harm to the fetus due to rabeprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Following intravenous administration of ¹⁴C-labeled rabeprazole to lactating rats, radioactivity in milk reached levels that were 2- to 7-fold higher than levels in the blood. It is not known if unmetabolized rabeprazole is excreted in human breast milk. Administration of rabeprazole to rats in late gestation and during lactation at doses of 400 mg/kg/day (about 195-times the human dose based on mg/m²) resulted in decreases in body weight gain of the pups. Since many drugs are excreted in milk, and because of the potential for adverse reactions to nursing infants from rabeprazole, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and efficacy of rabeprazole in pediatric patients has not been established.

References:

1. Pantoflickova D, Dorta G, Jornod P, et al. Identification of the characteristics influencing the degree of antisecretory activity of PPIs [abstract]. *Gastroenterology*. 2000;118:A5895.
2. Data on file, Eisai Inc.

Manufactured by Eisai Co., Ltd., Misato, Japan
Made in Japan

Marketed by



Teaneck, NJ 07666

Marketed by



Titusville, NJ 08560-0200

Use in Women

Duodenal ulcer and erosive esophagitis healing rates in women are similar to those in men. Adverse events and laboratory test abnormalities in women occurred at rates similar to those in men.

Geriatric Use

The total number of subjects in clinical studies of ACIPHEX® 19% were 65 years and over, while 4% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Worldwide, over 2900 patients have been treated with rabeprazole in Phase II-III clinical trials involving various dosages and durations of treatment. In general, rabeprazole treatment has been well-tolerated in both short-term and long-term trials. The adverse events rates were generally similar between the 10 and 20 mg doses.

Incidence in Controlled North American and European Clinical Trials

In an analysis of adverse events assessed as possibly or probably related to treatment appearing in greater than 1% of ACIPHEX® patients and appearing with greater frequency than placebo in controlled North American and European trials, the incidence of headache was 2.4% (n=1552) for ACIPHEX® versus 1.6% (n=258) for placebo.

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Laboratory Values: The following changes in laboratory parameters were reported as adverse events: abnormal platelets, albuminuria, creatine phosphokinase increased, erythrocytes abnormal, hypercholesterolemia, hyperglycemia, hyperlipemia, hypokalemia, hyponatremia, leukocytosis, leukorrhea, liver function tests abnormal, prostatic specific antigen increase, SGPT increased, urine abnormality, WBC abnormal.

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Post-Marketing Adverse Events: Additional adverse events reported from worldwide marketing experience with rabeprazole sodium are: sudden death, coma and hyperammonemia, jaundice, rhabdomyolysis, disorientation and delirium, bulbar and other drug eruptions of the skin, interstitial pneumonia, and TSH elevations. In most instances, the relationship to rabeprazole sodium was unclear. In addition, agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, and thrombocytopenia have been reported.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug. There has been no experience with large overdoses with rabeprazole. Seven reports of accidental overdose with rabeprazole have been received. The maximum reported overdose was 80 mg. There were no clinical signs or symptoms associated with any reported overdose. Patients with Zollinger-Ellison syndrome have been treated with up to 120 mg rabeprazole QD. No specific antidote for rabeprazole is known. Rabeprazole is extensively protein bound and is not readily dialyzed. In the event of overdose, treatment should be symptomatic and supportive.

Single oral doses of rabeprazole at 786 mg/kg and 1024 mg/kg were lethal to mice and rats, respectively. The single oral dose of 2000 mg/kg was not lethal to dogs. The major symptoms of acute toxicity were hypoadaptivity, labored respiration, lateral or prone position and convulsion in mice and rats and watery diarrhea, tremor, convulsion and coma in dogs.

DOSE AND ADMINISTRATION

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily for four to eight weeks. (See INDICATIONS AND USAGE). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX® may be considered.

Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD Maintenance)

The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily. (See INDICATIONS AND USAGE).

Healing of Duodenal Ulcers

The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily after the morning meal for a period up to four weeks. (See INDICATIONS AND USAGE). Most patients with duodenal ulcer heal within four weeks. A few patients may require additional therapy to achieve healing.

Treatment of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

The dosage of ACIPHEX® in patients with pathologic hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Some patients may require divided doses. Doses up to 100 mg QD and 60 mg BID have been administered. Some patients with Zollinger-Ellison syndrome have been treated continuously with ACIPHEX® for up to one year.

No dosage adjustment is necessary in elderly patients, in patients with renal disease or in patients with mild to moderate hepatic impairment. Administration of rabeprazole to patients with mild to moderate liver impairment resulted in increased exposure and decreased elimination. Due to the lack of clinical data on rabeprazole in patients with severe hepatic impairment, caution should be exercised in those patients.

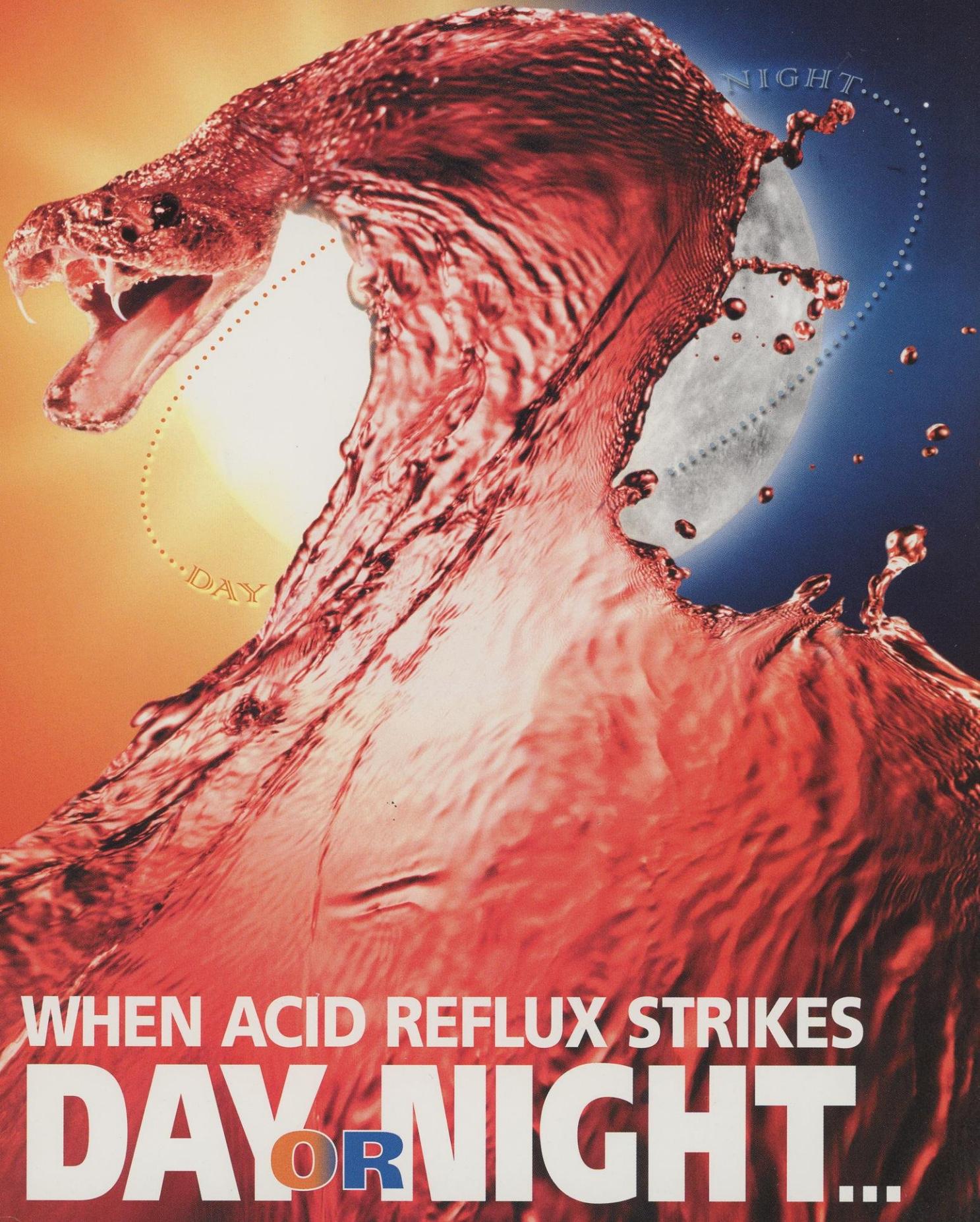
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01-AK-259

IN ACID SUPPRESSION
FOR EROSION GERD



WHEN ACID REFLUX STRIKES
DAY OR NIGHT...



Please see brief summary of prescribing information
at the end of this advertisement.

STRIKE BACK NOW DAY OR NIGHT

ONCE-A-DAY

WITH

AcipHex®

rabeprazole sodium

20-MG TABLETS

The proton pump inhibitor with:

Proven control

- Potent, first-dose acid control for a full 24 hours¹

Significant symptom relief day or night²

- **Daytime** heartburn relief reported by approximately **80%** of patients on day 1 and approximately **95%** of patients on day 28*
- **Nighttime** heartburn relief reported by approximately **80%** of patients on day 1 and approximately **95%** of patients on day 28*

Excellent safety

- In clinical trials the most common side effect assessed as possibly related to ACIPHEX was headache (2.4% vs 1.6% for placebo)
- *Symptomatic response to therapy does not preclude the presence of gastric malignancy. ACIPHEX is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles, or to any component of the formulation*

*Erosive GERD patients with moderate to severe symptoms at baseline who achieved mild or no symptoms during treatment in a large, open-label, multicenter study (n=1449 daytime; n=1469 nighttime).

STRIKE BACK NOW

VISIT US AT
WWW.ACIPHEX.COM

Before prescribing, please consult complete prescribing information of which the following is a brief summary.

INDICATIONS AND USAGE

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

ACIPHEX® is indicated for short-term (4 to 8 weeks) treatment in the healing and symptomatic relief of erosive or ulcerative gastroesophageal reflux disease (GERD). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX® may be considered.

Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

ACIPHEX® is indicated for maintaining healing and reduction in relapse rates of heartburn symptoms in patients with erosive or ulcerative gastroesophageal reflux disease (GERD Maintenance).

Healing of Duodenal Ulcers

ACIPHEX® is indicated for short-term (up to 4 weeks) treatment in the healing and symptomatic relief of duodenal ulcers. Most patients heal within four weeks.

Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome

ACIPHEX® is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.

CONTRAINDICATIONS

Rabeprazole is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles or to any component of the formulation.

PRECAUTIONS

General

Symptomatic response to therapy with rabeprazole does not preclude the presence of gastric malignancy.

Patients with healed GERD were treated for up to 40 months with rabeprazole and monitored with serial gastric biopsies. Patients without *H. pylori* infection (221 of 326 patients) had no clinically important pathologic changes in the gastric mucosa. Patients with *H. pylori* infection at baseline (105 of 326 patients) had mild or moderate inflammation in the gastric body or mild inflammation in the gastric antrum. Patients with mild grades of infection or inflammation in the gastric body tended to change to moderate, whereas those graded moderate at baseline tended to remain stable. Patients with mild grades of infection or inflammation in the gastric antrum tended to remain stable. At baseline 8% of patients had atrophy of glands in the gastric body and 15% had atrophy in the gastric antrum. At endpoint, 15% of patients had atrophy of glands in the gastric body and 11% had atrophy in the gastric antrum. Approximately 4% of patients had intestinal metaplasia at some point during follow-up, but no consistent changes were seen.

Information for Patients

Patients should be cautioned that ACIPHEX® delayed-release tablets should be swallowed whole. The tablets should not be chewed, crushed, or split.

Drug Interactions

Rabeprazole is metabolized by the cytochrome P450 (CYP450) drug metabolizing enzyme system. Studies in healthy subjects have shown that rabeprazole does not have clinically significant interactions with other drugs metabolized by the CYP450 system, such as warfarin and theophylline given as single oral doses, diazepam as a single intravenous dose, and phenytoin given as a single intravenous dose (with supplemental oral dosing). *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporine metabolism with an IC_{50} of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days of dosing with 20 mg of rabeprazole. This degree of inhibition is similar to that by omeprazole at equivalent concentrations.

Rabeprazole produces sustained inhibition of gastric acid secretion. An interaction with compounds which are dependent on gastric pH for absorption may occur due to the magnitude of acid suppression observed with rabeprazole. For example, in normal subjects, coadministration of rabeprazole 20 mg OD resulted in an approximately 30% decrease in the bioavailability of ketoconazole and increases in the AUC and C_{max} for digoxin of 19% and 29%, respectively. Therefore, patients may need to be monitored when such drugs are taken concomitantly with rabeprazole. Co-administration of rabeprazole and antacids produced no clinically relevant changes in plasma rabeprazole concentrations.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 88/104-week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumor occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 $\mu\text{g}\cdot\text{hr}/\text{mL}$ which is 1.6 times the human exposure (plasma $AUC_{0-\infty} = 0.88 \mu\text{g}\cdot\text{hr}/\text{mL}$) at the recommended dose for GERD (20 mg/day). In a 104-week carcinogenicity study in Sprague-Dawley rats, males were treated with oral doses of 5, 15, 30, and 60 mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoma tumors in female rats at all doses including the lowest tested dose. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 $\mu\text{g}\cdot\text{hr}/\text{mL}$ which is about 0.1 times the human exposure at the recommended dose for GERD. In male rats, no treatment related tumors were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 $\mu\text{g}\cdot\text{hr}/\text{mL}$ (0.2 times the human exposure at the recommended dose for GERD).

Rabeprazole was positive in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward gene mutation test and the mouse lymphoma cell (L5178Y/TK+/−) forward gene mutation test. Its demethylated-metabolite was also positive in the Ames test. Rabeprazole was negative in the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test, and the *in vivo* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 $\mu\text{g}\cdot\text{hr}/\text{mL}$, about 10 times the human exposure at the recommended dose for GERD) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy

Teratogenic Effects. Pregnancy Category B: Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 $\mu\text{g}\cdot\text{hr}/\text{mL}$, about 13 times the human exposure at the recommended dose for GERD) and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 $\mu\text{g}\cdot\text{hr}/\text{mL}$, about 8 times the human exposure at the recommended dose for GERD) and have revealed no evidence of impaired fertility or harm to the fetus due to rabeprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Following intravenous administration of ^{14}C -labeled rabeprazole to lactating rats, radioactivity in milk reached levels that were 2- to 7-fold higher than levels in the blood. It is not known if unmetabolized rabeprazole is excreted in human breast milk. Administration of rabeprazole to rats in late gestation and during lactation at doses of 400 mg/kg/day (about 195-times the human dose based on mg/m²) resulted in decreases in body weight gain of the pups. Since many drugs are excreted in milk, and because of the potential for adverse reactions to nursing infants from rabeprazole, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and efficacy of rabeprazole in pediatric patients has not been established.

References:

1. Pantoflickova D, Dorta G, Jomod P, et al. Identification of the characteristics influencing the degree of antisecretory activity of PPIs [abstract]. *Gastroenterology*. 2000;118:A5895.
2. Data on file, Eisai Inc.

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Use in Women

Duodenal ulcer and erosive esophagitis healing rates in women are similar to those in men. Adverse events and laboratory test abnormalities in women occurred at rates similar to those in men.

Geriatric Use

Of the total number of subjects in clinical studies of ACIPHEX®, 19% were 65 years and over, while 4% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Worldwide, over 2900 patients have been treated with rabeprazole in Phase II-III clinical trials involving various dosages and durations of treatment. In general, rabeprazole treatment has been well-tolerated in both short-term and long-term trials. The adverse events rates were generally similar between the 10 and 20 mg doses.

Incidence in Controlled North American and European Clinical Trials

In an analysis of adverse events assessed as possibly or probably related to treatment appearing in greater than 1% of ACIPHEX® patients and appearing with greater frequency than placebo in controlled North American and European trials, the incidence of headache was 2.4% (n=1552) for ACIPHEX® versus 1.6% (n=258) for placebo.

In short and long-term studies, the following adverse events, regardless of causality, were reported in ACIPHEX®-treated patients. Rare events are those reported in $\leq 1/1000$ patients.

Body as a Whole: asthenia, fever, allergic reaction, chills, malaise, chest pain substernal, neck rigidity, photosensitivity reaction. **Rare:** abdomen enlarged, face edema, hangover effect. **Cardiovascular System:** hypertension, myocardial infarct, electrocardiogram abnormal, migraine, syncope, angina pectoris, bundle branch block, palpitation, sinus bradycardia, tachycardia. **Rare:** bradycardia, pulmonary embolus, supraventricular tachycardia, thromboembolitis, vasodilation, QTc prolongation and ventricular tachycardia. **Digestive System:** diarrhea, nausea, abdominal pain, vomiting, dyspepsia, flatulence, constipation, dry mouth, eructation, gastroenteritis, rectal hemorrhage, melena, anorexia, cholelithiasis, mouth ulceration, stomatitis, dysphagia, gingivitis, cholecytis, increased appetite, abnormal stools, colitis, esophagitis, glossitis, pancreatitis, proctitis. **Rare:** bloody diarrhea, cholangitis, duodenitis, gastrointestinal hemorrhage, hepatic encephalopathy, hepatitis, hepatoma, liver fatty deposit, salivary gland enlargement, thirst. **Endocrine System:** hyperthyroidism, hypothyroidism. **Hemic & Lymphatic System:** anemia, ecchymosis, lymphadenopathy, hypochromic anemia. **Musculo-Skeletal System:** myalgia, arthritis, leg cramps, bone pain, arthrosis, bursitis. **Rare:** twitching. **Nervous System:** insomnia, anxiety, dizziness, depression, nervousness, somnolence, hypertonnia, neuromuscular, neuralgia, vertigo, convolution, abnormal dreams, libido decreased, neuropathy, paresthesia, tremor. **Rare:** agitation, amnesia, confusion, extrapyramidal syndrome, hyperkinesia. **Respiratory System:** dyspnea, asthma, epistaxis, laryngitis, hiccup, hyperventilation. **Rare:** apnea, hypoventilation. **Skin and Appendages:** rash, pruritus, sweating, urticaria, alopecia. **Rare:** dry skin, herpes zoster, psoriasis, skin discoloration. **Special Senses:** cataract, amblyopia, glaucoma, dry eyes, abnormal vision, tinnitus, otitis media. **Rare:** corneal opacity, blurry vision, diplopia, deafness, eye pain, renal degeneration, strabismus. **Urogenital System:** cystitis, urinary frequency, dysmenorrhea, dysuria, kidney calculus, metrorrhagia, polyuria. **Rare:** breast enlargement, hematuria, impotence, leukorrhea, menorrhagia, orchitis, urinary incontinence. **Laboratory Values:** The following changes in laboratory parameters were reported as adverse events: abnormal platelets, albuminuria, creatine phosphokinase increased, erythrocytes abnormal, hypercholesterolemia, hyperglycemia, hyperlipemia, hypokalemia, hyponatremia, leukocytosis, leukorrhea, liver function tests abnormal, prostatic specific antigen increase, SGPT increased, urine abnormality, WBC abnormal.

In controlled clinical studies, 3/1456 (0.2%) patients treated with rabeprazole and 2/237 (0.8%) patients treated with placebo developed treatment-emergent abnormalities (which were either new on study or present at study entry with an increase of 1.25 x baseline value) in SGOT (AST), SGPT (ALT), or both. None of the three rabeprazole patients experienced chills, fever, right upper quadrant pain, nausea or jaundice.

Post-Marketing Adverse Events: Additional adverse events reported from worldwide marketing experience with rabeprazole sodium are: sudden death, coma and hyperammonemia, jaundice, rhabdomyolysis, disorientation and delirium, bullous and other drug eruptions of the skin, interstitial pneumonia, and TSH elevations. In most instances, the relationship to rabeprazole sodium was unclear. In addition, agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, and thrombocytopenia have been reported.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug. There has been no experience with large overdoses with rabeprazole. Seven reports of accidental overdose with rabeprazole have been received. The maximum reported overdose was 80 mg. There were no clinical signs or symptoms associated with any reported overdose. Patients with Zollinger-Ellison syndrome have been treated with up to 120 mg rabeprazole QD. No specific antidote for rabeprazole is known. Rabeprazole is extensively protein bound and is not readily dialyzable. In the event of overdose, treatment should be symptomatic and supportive. Single oral doses of rabeprazole at 786 mg/kg and 1024 mg/kg were lethal to mice and rats, respectively. The single oral dose of 2000 mg/kg was not lethal to dogs. The major symptoms of acute toxicity were hyporeactivity, labored respiration, lateral or prone position and convolution in mice and rats and watery diarrhea, tremor, convolution and coma in dogs.

DOSE AND ADMINISTRATION

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily for four to eight weeks. (See INDICATIONS AND USAGE). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX® may be considered.

Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD Maintenance)

The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily. (See INDICATIONS AND USAGE).

Healing of Duodenal Ulcers

The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily after the morning meal for a period up to four weeks. (See INDICATIONS AND USAGE). Most patients with duodenal ulcer heal within four weeks. A few patients may require additional therapy to achieve healing.

Treatment of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

The dosage of ACIPHEX® in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Some patients may require divided doses. Doses up to 100 mg QD and 60 mg BID have been administered. Some patients with Zollinger-Ellison syndrome have been treated continuously with ACIPHEX® for up to one year.

No dosage adjustment is necessary in elderly patients, in patients with renal disease or in patients with mild to moderate hepatic impairment. Administration of rabeprazole to patients with mild to moderate liver impairment resulted in increased exposure and decreased elimination. Due to the lack of clinical data on rabeprazole in patients with severe hepatic impairment caution should be exercised in those patients.

ACIPHEX® tablets should be swallowed whole. The tablets should not be chewed, crushed, or split.



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01-AX-260R

May 2001

Printed in USA

IN ACID SUPPRESSION FOR EROSIONAL GERD

STRIKE BACK NOW

**DAY
OR
NIGHT**

WITH

ONCE-A-DAY

AcipHex®
rabeprazole sodium
20-MG TABLETS

A proton pump inhibitor with:

- Potent 24-hour acid control with the first dose¹
- Significant symptom relief day or night²
- An excellent safety profile

The most common side effect assessed as possibly related to ACIPHEX was headache (2.4% vs 1.6% for placebo).

Symptomatic response to therapy does not preclude the presence of gastric malignancy. ACIPHEX is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles, or to any component of the formulation.

Please see brief summary of prescribing information at the end of this advertisement.

STRIKE BACK NOW

Before prescribing, please consult complete prescribing information of which the following is a brief summary.

INDICATIONS AND USAGE

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

ACIPHEX® is indicated for short-term (4 to 8 weeks) treatment in the healing and symptomatic relief of erosive or ulcerative gastroesophageal reflux disease (GERD). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX® may be considered.

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CONTRAINDICATIONS

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PRECAUTIONS

General

Symptomatic response to therapy with rabeprazole does not preclude the presence of gastric malignancy.

Patients with healed GERD were treated for up to 40 months with rabeprazole and monitored with serial gastric biopsies. Patients without *H. pylori* infection (221 of 326 patients) had no clinically important pathologic changes in the gastric mucosa. Patients with *H. pylori* infection at baseline (105 of 326 patients) had mild or moderate inflammation in the gastric body or mild inflammation in the gastric antrum. Patients with mild grades of infection or inflammation in the gastric body tended to change to moderate, whereas those graded moderate at baseline tended to remain stable. Patients with mild grades of infection or inflammation in the gastric antrum tended to remain stable. At baseline 8% of patients had atrophy of glands in the gastric body and 15% had atrophy in the gastric antrum. At endpoint, 15% of patients had atrophy of glands in the gastric body and 11% had atrophy in the gastric antrum. Approximately 4% of patients had intestinal metaplasia at some point during follow-up, but no consistent changes were seen.

Information for Patients

Patients should be cautioned that ACIPHEX® delayed-release tablets should be swallowed whole. The tablets should not be chewed, crushed, or split.

Drug Interactions

Rabeprazole is metabolized by the cytochrome P450 (CYP450) drug metabolizing enzyme system. Studies in healthy subjects have shown that rabeprazole does not have clinically significant interactions with other drugs metabolized by the CYP450 system, such as warfarin and theophylline given as single oral doses, diazepam as a single intravenous dose, and phenytoin given as a single intravenous dose (with supplemental oral dosing). *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporine metabolism with an IC₅₀ of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days of dosing with 20 mg of rabeprazole. This degree of inhibition is similar to that of omeprazole at equivalent concentrations.

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In a 88/104-week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumor occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 $\mu\text{g}\cdot\text{hr}/\text{mL}$ which is 1.6 times the human exposure (plasma AUC₀₋₂₄ = 0.88 $\mu\text{g}\cdot\text{hr}/\text{mL}$) at the recommended dose for GERD (20 mg/day). In a 104-week carcinogenicity study in Sprague-Dawley rats, males were treated with oral doses of 5, 15, 30 and 60 mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumors in female rats at all doses including the lowest tested dose. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 $\mu\text{g}\cdot\text{hr}/\text{mL}$ which is about 0.1 times the human exposure at the recommended dose for GERD. In male rats, no treatment related tumors were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 $\mu\text{g}\cdot\text{hr}/\text{mL}$ (0.2 times the human exposure at the recommended dose for GERD).

Rabeprazole was positive in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward gene mutation test and the mouse lymphoma cell (L5178Y/TK⁺) forward gene mutation test. Its demethylated-metabolite was also positive in the Ames test. Rabeprazole was negative in the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test, and the *in vivo* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

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Teratogenic Effects. Pregnancy Category B: Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 $\mu\text{g}\cdot\text{hr}/\text{mL}$, about 13 times the human exposure at the recommended dose for GERD) and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 $\mu\text{g}\cdot\text{hr}/\text{mL}$, about 8 times the human exposure at the recommended dose for GERD) and have revealed no evidence of impaired fertility or harm to the fetus due to rabeprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Following intravenous administration of ¹⁴C-labeled rabeprazole to lactating rats, radioactivity in milk reached levels that were 2- to 7-fold higher than levels in the blood. It is not known if unmetabolized rabeprazole is excreted in human breast milk. Administration of rabeprazole to rats in late gestation and during lactation at doses of 400 mg/kg/day (about 195-times the human dose based on mg/m²) resulted in decreases in body weight gain of the pups. Since many drugs are excreted in milk, and because of the potential for adverse reactions to nursing infants from rabeprazole, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of rabeprazole in pediatric patients have not been established.

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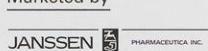
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Use in Women

Duodenal ulcer and erosive esophagitis healing rates in women are similar to those in men. Adverse events and laboratory test abnormalities in women occurred at rates similar to those in men.

Geriatric Use

Of the total number of subjects in clinical studies of ACIPHEX®, 19% were 65 years and over, while 4% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Worldwide, over 2900 patients have been treated with rabeprazole in Phase II-III clinical trials involving various dosages and durations of treatment. In general, rabeprazole treatment has been well-tolerated in both short-term and long-term trials. The adverse events rates were generally similar between the 10 and 20 mg doses.

Incidence in Controlled North American and European Clinical Trials

In an analysis of adverse events assessed as possibly or probably related to treatment appearing in greater than 1% of ACIPHEX® patients and appearing with greater frequency than placebo in controlled North American and European trials, the incidence of headache was 2.4% (n=1552) for ACIPHEX® versus 1.6% (n=258) for placebo. In short and long-term studies, the following adverse events, regardless of causality, were reported in ACIPHEX®-treated patients. Rare events are those reported in $\leq 1/1000$ patients.

Body as a Whole: asthenia, fever, allergic reaction, chills, malaise, chest pain substernal, neck rigidity, photosensitivity reaction. Rare: abdomen enlarged, face edema, hangover effect. **Cardiovascular System:** hypertension, myocardial infarct, electrocardiogram abnormal, migraine, syncope, angina pectoris, bundle branch block, palpitation, sinus bradycardia, tachycardia. Rare: bradycardia, pulmonary embolus, supraventricular tachycardia, thrombophlebitis, vasodilation, QTc prolongation and ventricular tachycardia. **Digestive System:** diarrhea, nausea, abdominal pain, vomiting, dyspepsia, flatulence, constipation, dry mouth, eructation, gastritis, rectal hemorrhage, melena, anorexia, cholelithiasis, mouth ulceration, stomatitis, dysphagia, gingivitis, cholecystitis, increased appetite, abnormal stools, colitis, esophagitis, glossitis, pancreatitis, proctitis. Rare: bloody diarrhea, cholangitis, duodenitis, gastrointestinal hemorrhage, hepatic encephalopathy, hepatitis, hepatoma, liver fatty deposit, salivary gland enlargement, thirst. **Endocrine System:** hyperthyroidism, hypothyroidism. **Hemic / Lymphatic System:** anemia, ecchymosis, lymphadenopathy, hypochromic anemia. **Metabolic & Nutritional Disorders:** peripheral edema, edema, weight gain, gout, dehydration, weight loss. **Musculo-Skeletal System:** myalgia, arthritis, leg cramps, bone pain, arthrosis, bursitis. Rare: twitching. **Nervous System:** insomnia, anxiety, dizziness, depression, nervousness, somnolence, hypertension, neuralgia, vertigo, convulsion, abnormal dreams, libido decreased, neuropathy, paresthesia, tremor. Rare: agitation, amnesia, confusion, extrapyramidal syndrome, hyperkinesia. **Respiratory System:** dyspnea, asthma, epistaxis, laryngitis, hiccup, hyperventilation. Rare: apnea, hypoventilation. **Skin and Appendages:** rash, pruritis, sweating, urticaria, alopecia. Rare: dry skin, herpes zoster, psoriasis, skin discoloration. **Special Senses:** cataract, amblyopia, glaucoma, dry eyes, abnormal vision, tinnitus, otitis media. Rare: corneal opacity, blurry vision, diplopia, deafness, eye pain, retinal degeneration, strabismus. **Urogenital System:** cystitis, urinary frequency, dysmenorrhea, dysuria, kidney calculus, metrorrhagia, polyuria. Rare: breast enlargement, hematuria, impotence, leukorrhea, menorrhagia, orchitis, urinary incontinence.

Laboratory Values: The following changes in laboratory parameters were reported as adverse events: abnormal platelets, albuminuria, creatine phosphokinase increased, erythrocytes abnormal, hypercholesterolemia, hyperglycemia, hyperlipemia, hypokalemia, hyponatremia, leukocytosis, leukorrhea, liver function tests abnormal, prostatic specific antigen increase, SGPT increased, urine abnormality, WBC abnormal.

In controlled clinical studies, 3/1456 (0.2%) patients treated with rabeprazole and 2/237 (0.8%) patients treated with placebo developed treatment-emergent abnormalities (which were either new on study or present at study entry with an increase of 1.25 x baseline value) in SGOT (AST), SGPT (ALT), or both. None of the three rabeprazole patients experienced chills, fever, right upper quadrant pain, nausea or jaundice.

Post-Marketing Adverse Events: Additional adverse events reported from worldwide marketing experience with rabeprazole sodium are: sudden death, coma and hyperammonemia, jaundice, rhabdomyolysis, disorientation and delirium, anaphylaxis, angioedema, bullous and other drug eruptions of the skin, interstitial pneumonia, and TSH elevations. In most instances, the relationship to rabeprazole sodium was unclear. In addition, agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, and thrombocytopenia have been reported.

OVERDOSES: Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug. There has been no experience with large overdoses with rabeprazole. Seven reports of accidental overdosage with rabeprazole have been received. The maximum reported overdose was 80 mg. There were no clinical signs or symptoms associated with any reported overdose. Patients with Zollinger-Ellison syndrome have been treated with up to 120 mg rabeprazole QD. No specific antidote for rabeprazole is known. Rabeprazole is extensively protein bound and is not readily dialyzable. In the event of overdose, treatment should be symptomatic and supportive. Single oral doses of rabeprazole at 786 mg/kg and 1024 mg/kg were lethal to mice and rats, respectively. The single oral dose of 2000 mg/kg was not lethal to dogs. The major symptoms of acute toxicity were hypoactivity, labored respiration, lateral or prone position and convulsion in mice and rats and watery diarrhea, tremor, convolution and coma in dogs.

DOSAGE AND ADMINISTRATION

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily for four to eight weeks. (See INDICATIONS AND USAGE). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX® may be considered.

Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD Maintenance)

The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily. (See INDICATIONS AND USAGE).

Healing of Duodenal Ulcers

The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily after the morning meal for a period up to four weeks. (See INDICATIONS AND USAGE). Most patients with duodenal ulcer heal within four weeks. A few patients may require additional therapy to achieve healing.

Treatment of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

The dosage of ACIPHEX® in patients with pathologic hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue as long as clinically indicated. Some patients may require divided doses. Doses up to 100 mg QD and 60 mg BID have been administered. Some patients with Zollinger-Ellison syndrome have been treated continuously with ACIPHEX® for up to one year.

No dosage adjustment is necessary in elderly patients, in patients with renal disease or in patients with mild to moderate hepatic impairment. Administration of rabeprazole to patients with mild to moderate liver impairment resulted in increased exposure and decreased elimination. Due to the lack of clinical data on rabeprazole in patients with severe hepatic impairment, caution should be exercised in those patients.

ACIPHEX® tablets should be swallowed whole. The tablets should not be chewed, crushed, or split.

AX-25

ACIPHEX® is a registered trademark of Eisai Co., Ltd., Tokyo, Japan.

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01-AX-259

Dec. 2001

Printed in USA

IN ACID SUPPRESSION
FOR EROSIONAL GERD

WHEN ACID REFLUX
STRIKES...

STRIKE
BACK
NOW

WITH

ONCE-A-DAY

AcipHexTM
rabeprazole sodium
20-MG TABLETS

A proton pump inhibitor with:

- Proven acid suppression in erosive GERD
- Excellent safety profile

The most common side effect assessed as possibly related to ACIPHEX was headache (2.4% vs 1.6% for placebo).

Symptomatic response to therapy does not preclude the presence of gastric malignancy. ACIPHEX is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles, or to any component of the formulation.

Please see brief summary of prescribing information at the end of this advertisement.

STRIKE BACK NOW

Before prescribing, please consult complete prescribing information of which the following is a brief summary.

INDICATIONS AND USAGE

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

ACIPHEX™ is indicated for short-term (4 to 8 weeks) treatment in the healing and symptomatic relief of erosive or ulcerative gastroesophageal reflux disease (GERD). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX™ may be considered.

Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

ACIPHEX™ is indicated for maintaining healing and reduction in relapse rates of heartburn symptoms in patients with erosive or ulcerative gastroesophageal reflux disease (GERD) Maintenance.

Healing of Duodenal Ulcers

ACIPHEX™ is indicated for short-term (up to four weeks) treatment in the healing and symptomatic relief of duodenal ulcers. Most patients heal within four weeks.

Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome

ACIPHEX™ is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.

CONTRAINdications

Rabeprazole is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles or to any component of the formulation.

PRECAUTIONS

General

Symptomatic response to therapy with rabeprazole does not preclude the presence of gastric malignancy.

Patients with healed GERD were treated for up to 40 months with rabeprazole and monitored with serial gastric biopsies. Patients without *H. pylori* infection (221 of 326 patients) had no clinically important pathologic changes in the gastric mucosa. Patients with *H. pylori* infection at baseline (105 of 326 patients) had mild or moderate inflammation in the gastric body or mild inflammation in the gastric antrum. Patients with mild grades of infection or inflammation in the gastric body tended to change to moderate, whereas those graded moderate at baseline tended to remain stable. Patients with mild grades of infection or inflammation in the gastric antrum tended to remain stable. At baseline 8% of patients had atrophy of glands in the gastric body and 15% had atrophy in the gastric antrum. At endpoint, 15% of patients had atrophy of glands in the gastric body and 11% had atrophy in the gastric antrum. Approximately 4% of patients had intestinal metaplasia at some point during follow-up, but no consistent changes were seen.

Information for Patients

Patients should be cautioned that ACIPHEX™ delayed-release tablets should be swallowed whole. The tablets should not be chewed, crushed, or split.

Drug Interactions

Rabeprazole is metabolized by the cytochrome P450 (CYP450) drug metabolizing enzyme system. Studies in healthy subjects have shown that rabeprazole does not have clinically significant interactions with other drugs metabolized by the CYP450 system, such as warfarin and theophylline given as single oral doses, diazepam as a single intravenous dose, and phenytoin given as a single intravenous dose (with supplemental oral dosing). *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporine metabolism with an IC_{50} of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days of dosing with 20 mg of rabeprazole. This degree of inhibition is similar to that by omeprazole at equivalent concentrations.

Rabeprazole produces sustained inhibition of gastric acid secretion. An interaction with compounds which are dependent on gastric pH for absorption may occur due to the magnitude of acid suppression observed with rabeprazole. For example, in normal subjects, coadministration of rabeprazole 20 mg QD resulted in an approximately 30% decrease in the bioavailability of ketoconazole and increases in the AUC and C_{max} for digoxin of 19% and 29%, respectively. Therefore, patients may need to be monitored when such drugs are taken concomitantly with rabeprazole. Co-administration of rabeprazole and antacids produced no clinically relevant changes in plasma rabeprazole concentrations.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 88/104-week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumor occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 μ g·hr/mL which is 1.6 times the human exposure (plasma $AUC_{0-24} = 0.88 \mu$ g·hr/mL) at the recommended dose for GERD (20 mg/day). In a 104-week carcinogenicity study in Sprague-Dawley rats, males were treated with oral doses of 5, 15, 30 and 60 mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumors in female rats at all doses including the lowest tested dose. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 μ g·hr/mL which is about 0.1 times the human exposure at the recommended dose for GERD. In male rats, no treatment related tumors were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 μ g·hr/mL (0.2 times the human exposure at the recommended dose for GERD).

Rabeprazole was positive in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward gene mutation test and the mouse lymphoma cell (L5178Y/TK+) forward gene mutation test. Its demethylated-metabolite was also positive in the Ames test. Rabeprazole was negative in the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test, and the *in vivo* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 μ g·hr/mL, about 10 times the human exposure at the recommended dose for GERD) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy

Teratogenic Effects. Pregnancy Category B: Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 μ g·hr/mL, about 13 times the human exposure at the recommended dose for GERD) and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 μ g·hr/mL, about 8 times the human exposure at the recommended dose for GERD) and have revealed no evidence of impaired fertility or harm to the fetus due to rabeprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Following intravenous administration of ¹⁴C-labeled rabeprazole to lactating rats, radioactivity in milk reached levels that were 2- to 7-fold higher than levels in the blood. It is not known if unmetabolized rabeprazole is excreted in human breast milk. Administration of rabeprazole to rats in late gestation and during lactation at doses of 400 mg/kg/day (about 195-times the human dose based on mg/m²) resulted in decreases in body weight gain of the pups. Since many drugs are excreted in milk, and because of the potential for adverse reactions to nursing infants from rabeprazole, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and efficacy of rabeprazole in pediatric patients has not been established.

Use in Women

Duodenal ulcer and erosive esophagitis healing rates in women are similar to those in men. Adverse events and laboratory test abnormalities in women occurred at rates similar to those in men.

Geriatric Use

Of the total number of subjects in clinical studies of ACIPHEX™, 19% were 65 years and over, while 4% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Worldwide, over 2900 patients have been treated with rabeprazole in Phase II-III clinical trials involving various dosages and durations of treatment. In general, rabeprazole treatment has been well-tolerated in both short-term and long-term trials. The adverse events rates were generally similar between the 10 and 20 mg doses.

Incidence in Controlled North American and European Clinical Trials

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In controlled clinical studies, 3/1456 (0.2%) patients treated with rabeprazole and 2/237 (0.8%) patients treated with placebo developed treatment-emergent abnormalities (which were either new on study or present at study entry with an increase of 1.25 x baseline value) in SGOT (AST), SGPT (ALT), or both. None of the three rabeprazole patients experienced chills, fever, right upper quadrant pain, nausea or jaundice.

Post-Marketing Adverse Events: Additional adverse events reported from worldwide marketing experience with rabeprazole sodium are: sudden death, coma and hyperammonemia, jaundice, rhabdomyolysis, disorientation and delirium, bullous and other drug eruptions of the skin, interstitial pneumonia, and TSH elevations. In most instances, the relationship to rabeprazole sodium was unclear. In addition, agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, and thrombocytopenia have been reported.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug. There has been no experience with large overdoses with rabeprazole. Seven reports of accidental overdose with rabeprazole have been received. The maximum reported overdose was 80 mg. There were no clinical signs or symptoms associated with any reported overdose. Patients with Zollinger-Ellison syndrome have been treated with up to 120 mg rabeprazole QD. No specific antidote for rabeprazole is known. Rabeprazole is extensively protein bound and is not readily dialyzable. In the event of overdose, treatment should be symptomatic and supportive. Single oral doses of rabeprazole at 786 mg/kg and 1024 mg/kg were lethal to mice and rats, respectively. The single oral dose of 2000 mg/kg was not lethal to dogs. The major symptoms of acute toxicity were hypoactivity, labored respiration, lateral or prone position and convulsion in mice and rats and watery diarrhea, tremor, convulsion and coma in dogs.

DOSAGE AND ADMINISTRATION

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

The recommended adult oral dose is one ACIPHEX™ 20 mg delayed-release tablet to be taken once daily for four to eight weeks. (See INDICATIONS AND USAGE). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX™ may be considered.

Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD Maintenance)

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Healing of Duodenal Ulcers

The recommended adult oral dose is one ACIPHEX™ 20 mg delayed-release tablet to be taken once daily after the morning meal for a period up to four weeks. (See INDICATIONS AND USAGE). Most patients with duodenal ulcer heal within four weeks. A few patients may require additional therapy to achieve healing.

Treatment of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

The dosage of ACIPHEX™ in patients with pathologic hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Some patients may require divided doses. Doses up to 100 mg QD and 60 mg BID have been administered. Some patients with Zollinger-Ellison syndrome have been treated continuously with ACIPHEX™ for up to one year.

No dosage adjustment is necessary in elderly patients, in patients with renal disease or in patients with mild to moderate hepatic impairment. Administration of rabeprazole to patients with mild to moderate liver impairment resulted in increased exposure and decreased elimination. Due to the lack of clinical data on rabeprazole in patients with severe hepatic impairment, caution should be exercised in those patients.

ACIPHEX™ tablets should be swallowed whole. The tablets should not be chewed, crushed, or split.



Manufactured by Eisai Co., Ltd., Misato, Japan
Made in Japan

Marketed by



Teaneck, NJ 07666

Marketed by



Titusville, NJ 08560-0200

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01-AX-094

IN EROSIONAL GERD

HIT HEARTBURN HARD



ACIPHEX® — 24-hour acid control
from the first dose

- Symptom relief on day 1*¹
- All-day, all-night acid control²
- An excellent safety profile

In clinical trials the most common side effect assessed as possibly related to ACIPHEX was headache (2.4% vs 1.6% for placebo).

Symptomatic response to therapy does not preclude the presence of gastric malignancy. ACIPHEX is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles, or to any component of the formulation. Patients treated with a proton pump inhibitor and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

ONCE-A-DAY

AcipHex®
rabeprazole sodium
20-MG TABLETS

*Erosive GERD patients with moderate to severe symptoms at baseline who achieved mild or no symptoms during treatment in a large, open-label, multicenter study (n=1449 daytime; n=1469 nighttime). Within 36 hours of the initial visit, patients began reporting the severity of their symptoms, including daytime and nighttime heartburn, for the first 7 days and on day 28.

Please see brief summary of prescribing information on adjacent page.

24-hour acid control from the first dose

AcipHex®

rabeprazole sodium

20-MG TABLETS

Before prescribing, please consult complete prescribing information of which the following is a brief summary.

INDICATIONS AND USAGE

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

ACIPHEX® is indicated for short-term (4 to 8 weeks) treatment in the healing and symptomatic relief of erosive or ulcerative gastroesophageal reflux disease (GERD). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX® may be considered.

Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

ACIPHEX® is indicated for maintaining healing and reduction in relapse rates of heartburn symptoms in patients with erosive or ulcerative gastroesophageal reflux disease (GERD Maintenance).

Healing of Duodenal Ulcers

ACIPHEX® is indicated for short-term (up to four weeks) treatment in the healing and symptomatic relief of duodenal ulcers. Most patients heal within four weeks.

Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome

ACIPHEX® is indicated for the long-term treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome.

CONTRAINdications

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PRECAUTIONS

General

Symptomatic response to therapy with rabeprazole does not preclude the presence of gastric malignancy.

Patients with healed GERD were treated for up to 40 months with rabeprazole and monitored with serial gastric biopsies. Patients without *H. pylori* infection (221 of 326 patients) had no clinically important pathologic changes in the gastric mucosa. Patients with *H. pylori* infection at baseline (105 of 326 patients) had mild or moderate inflammation in the gastric body or mild inflammation in the gastric antrum. Patients with mild grades of infection or inflammation in the gastric body tended to change to moderate, whereas those graded moderate at baseline tended to remain stable. Patients with mild grades of infection or inflammation in the gastric antrum tended to remain stable. At baseline 8% of patients had atrophy of glands in the gastric body and 15% had atrophy in the gastric antrum. At endpoint, 15% of patients had atrophy of glands in the gastric body and 11% had atrophy in the gastric antrum. Approximately 4% of patients had intestinal metaplasia at some point during follow-up, but no consistent changes were seen.

Information for Patients

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Drug Interactions

Rabeprazole is metabolized by the cytochrome P450 (CYP450) drug metabolizing enzyme system. Studies in healthy subjects have shown that rabeprazole does not have clinically significant interactions with other drugs metabolized by the CYP450 system, such as warfarin and theophylline given as single oral doses, diazepam as a single intravenous dose, and phenytoin given as a single intravenous dose (with supplemental oral dosing). *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporine metabolism with an IC_{50} of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days of dosing with 20 mg of rabeprazole. This degree of inhibition is similar to that by omeprazole at equivalent concentrations.

Rabeprazole produces sustained inhibition of gastric acid secretion. An interaction with compounds which are dependent on gastric pH for absorption may occur due to the magnitude of acid suppression observed with rabeprazole. For example, in normal subjects, co-administration of rabeprazole 20 mg QD resulted in an approximately 30% decrease in the bioavailability of ketoconazole and increases in the AUC and C_{max} for digoxin of 19% and 29%, respectively. Therefore, patients may need to be monitored when such drugs are taken concomitantly with rabeprazole. Co-administration of rabeprazole and antacids produced no clinically relevant changes in plasma rabeprazole concentrations.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 88/104-week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumor occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 μ g·hr/mL which is 1.6 times the human exposure (plasma $AUC_{0-\infty} = 0.88 \mu$ g·hr/mL) at the recommended dose for GERD (20 mg/day). In a 104-week carcinogenicity study in Sprague-Dawley rats, males were treated with oral doses of 5, 15, 30 and 60 mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumors in female rats at all doses including the lowest tested dose. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 μ g·hr/mL which is about 0.1 times the human exposure at the recommended dose for GERD. In male rats, no treatment related tumors were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 μ g·hr/mL (0.2 times the human exposure at the recommended dose for GERD).

Rabeprazole was positive in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward gene mutation test and the mouse lymphoma cell (L5178Y/TK+/−) forward gene mutation test. Its demethylated-metabolite was also positive in the Ames test. Rabeprazole was negative in the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test, and the *in vivo* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 μ g·hr/mL, about 10 times the human exposure at the recommended dose for GERD) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy

Teratogenic Effects. Pregnancy Category B: Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 μ g·hr/mL, about 13 times the human exposure at the recommended dose for GERD) and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 μ g·hr/mL, about 8 times the human exposure at the recommended dose for GERD) and have revealed no evidence of impaired fertility or harm to the fetus due to rabeprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Following intravenous administration of ¹⁴C-labeled rabeprazole to lactating rats, radioactivity in milk reached levels that were 2- to 7-fold higher than levels in the blood. It is not known if unmetabolized rabeprazole is excreted in human breast milk. Administration of rabeprazole to rats in late gestation and during lactation at doses of 400 mg/kg/day (about 195-times the human dose based on mg/m²) resulted in decreases in body weight gain of the pups. Since many drugs are excreted in milk, and because of the potential for adverse reactions to nursing infants from rabeprazole, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of rabeprazole in pediatric patients have not been established.

Use in Women

Duodenal ulcer and erosive esophagitis healing rates in women are similar to those in men. Adverse events and laboratory test abnormalities in women occurred at rates similar to those in men.

Geriatric Use

Of the total number of subjects in clinical studies of ACIPHEX®, 19% were 65 years and over, while 4% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Worldwide, over 2900 patients have been treated with rabeprazole in Phase II-III clinical trials involving various dosages and durations of treatment. In general, rabeprazole treatment has been well-tolerated in both short-term and long-term trials. The adverse events rates were generally similar between the 10 and 20 mg doses.

Incidence in Controlled North American and European Clinical Trials

In an analysis of adverse events assessed as possibly or probably related to treatment appearing in greater than 1% of ACIPHEX® patients and appearing with greater frequency than placebo in controlled North American and European trials, the incidence of headache was 2.4% (n=1552) for ACIPHEX® versus 1.6% (n=258) for placebo.

In short and long-term studies, the following adverse events, regardless of causality, were reported in ACIPHEX®-treated patients. Rare events are those reported in $\leq 1/1000$ patients.

Body as a Whole: asthenia, fever, allergic reaction, chills, malaise, chest pain substernal, neck rigidity, photosensitivity reaction. Rare: abdomen enlarged, face edema, hangover effect. **Cardiovascular System:** hypertension, myocardial infarct, electrocardiogram abnormal, migraine, syncope, angina pectoris, bundle branch block, palpitation, sinus bradycardia, tachycardia. Rare: bradycardia, pulmonary embolus, supraventricular tachycardia, thrombophlebitis, vasodilation, QTc prolongation and ventricular tachycardia. **Digestive System:** diarrhea, nausea, abdominal pain, vomiting, dyspepsia, flatulence, constipation, dry mouth, eructation, gastroenteritis, rectal hemorrhage, melena, anorexia, cholelithiasis, mouth ulceration, stomatitis, dysphagia, gingivitis, cholecystitis, increased appetite, abnormal stools, colitis, esophagitis, glossitis, pancreatitis, proctitis. Rare: bloody diarrhea, cholangitis, duodenitis, gastrointestinal hemorrhage, hepatic encephalopathy, hepatitis, hepatoma, liver fatty deposit, salivary gland enlargement, thirst. **Endocrine System:** hyperthyroidism, hypothyroidism. **Hemic & Lymphatic System:** anemia, ecchymosis, lymphadenopathy, hypochromic anemia. **Metabolic & Nutritional Disorders:** peripheral edema, edema, weight gain, gout, dehydration, weight loss. **Musculo-Skeletal System:** myalgia, arthritis, leg cramps, bone pain, arthrosis, bursitis. Rare: twitching. **Nervous System:** insomnia, anxiety, dizziness, depression, nervousness, somnolence, hypertension, neuralgia, vertigo, convulsion, abnormal dreams, libido decreased, neuropathy, paresthesia, tremor. Rare: agitation, amnesia, confusion, extrapyramidal syndrome, hyperkinesia. **Respiratory System:** dyspnea, asthma, epistaxis, laryngitis, hiccup, hyperventilation. Rare: apnea, hypoventilation. **Skin and Appendages:** rash, pruritus, sweating, urticaria, alopecia. Rare: dry skin, herpes zoster, psoriasis, skin discoloration. **Special Senses:** cataract, amblyopia, glaucoma, dry eyes, abnormal vision, tinnitus, otitis media. Rare: corneal opacity, blurry vision, diplopia, deafness, eye pain, retinal degeneration, strabismus. **Urogenital System:** cystitis, urinary frequency, dysmenorrhea, dysuria, kidney calculus, metrorrhagia, polyuria. Rare: breast enlargement, hematuria, impotence, leukorrhea, menorrhagia, orchitis, urinary incontinence.

Laboratory Values: The following changes in laboratory parameters were reported as adverse events: abnormal platelets, albuminuria, creatine phosphokinase increased, erythrocytes abnormal, hypercholesterolemia, hyperglycemia, hyperlipemia, hypokalemia, hypotremia, leukocytosis, leukorrhea, liver function tests abnormal, prostate specific antigen increase, SGPT increased, urine abnormality, WBC abnormal.

In controlled clinical studies, 3/1456 (0.2%) patients treated with rabeprazole and 2/237 (0.8%) patients treated with placebo developed treatment-emergent abnormalities (which were either new on study or present at study entry with an increase of 1.25 x baseline value) in SGOT (AST), SGPT (ALT), or both. None of the three rabeprazole patients experienced chills, fever, right upper quadrant pain, nausea or jaundice.

Post-Marketing Adverse Events: Additional adverse events reported from worldwide marketing experience with rabeprazole sodium are: sudden death, coma and hyperammonemia, jaundice, rhabdomyolysis, disorientation and delirium, anaphylaxis, angoedema, bullous and other drug eruptions of the skin, interstitial pneumonia, and TSH elevations. In most instances, the relationship to rabeprazole sodium was unclear. In addition, agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, and thrombocytopenia have been reported.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug. There has been no experience with large overdoses with rabeprazole. Seven reports of accidental overdoses with rabeprazole have been received. The maximum reported overdose was 80 mg. There were no clinical signs or symptoms associated with any reported overdose. Patients with Zollinger-Ellison syndrome have been treated with up to 120 mg rabeprazole QD. No specific antidote for rabeprazole is known. Rabeprazole is extensively protein bound and is not readily dialyzable. In the event of overdose, treatment should be symptomatic and supportive.

Single oral doses of rabeprazole at 786 mg/kg and 1024 mg/kg were lethal to mice and rats, respectively. The single oral dose of 2000 mg/kg was not lethal to dogs. The major symptoms of acute toxicity were hyporeactivity, labored respiration, lateral or prone position and convulsion in mice and rats and watery diarrhea, tremor, convulsion and coma in dogs.

DOSAGE AND ADMINISTRATION

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily for four to eight weeks. (See INDICATIONS AND USAGE). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX® may be considered.

Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD Maintenance)

The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily. (See INDICATIONS AND USAGE).

Healing of Duodenal Ulcers

The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily after the morning meal for a period up to four weeks. (See INDICATIONS AND USAGE). Most patients with duodenal ulcer heal within four weeks. A few patients may require additional therapy to achieve healing.

Treatment of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

The dosage of ACIPHEX® in patients with pathologic hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Some patients may require divided doses. Doses up to 100 mg QD and 60 mg BID have been administered. Some patients with Zollinger-Ellison syndrome have been treated continuously with ACIPHEX® for up to one year.

No dosage adjustment is necessary in elderly patients, in patients with renal disease or in patients with mild to moderate hepatic impairment. Administration of rabeprazole to patients with mild to moderate liver impairment resulted in increased exposure and decreased elimination. Due to the lack of clinical data on rabeprazole in patients with severe hepatic impairment, caution should be exercised in those patients.

ACIPHEX® tablets should be swallowed whole. The tablets should not be chewed, crushed, or split.

References:

1. Data on file, Eisai Inc.
2. Pantoflickova D, Dorta G, Jornod P, et al. Identification of the characteristics influencing the degree of antisecretory activity of PPIs [abstract]. *Gastroenterology*. 2000;118:A589.

ACIPHEX® is a registered trademark of Eisai Co., Ltd.

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ACIPHEX™: EXCELLENT SAFETY PROFILE

ACIPHEX:

Favorable drug-drug interaction profile

Drug Tested	warfarin	theophylline	diazepam	phenytoin
Drug Interaction	NO	NO	NO	NO

Like other proton pump inhibitors, ACIPHEX may have an interaction with compounds whose absorption depends on gastric pH, including ketoconazole and digoxin. Therefore, patients may need to be monitored when these medications are taken concomitantly.

- Over 4 years and 1.4 million patient months of worldwide clinical experience
- The most common side effect assessed as possibly related to ACIPHEX was headache (2.4% vs 1.6% for placebo)
- Symptomatic response to therapy does not preclude the presence of gastric malignancy. ACIPHEX is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles, or to any component of the formulation*

ACIPHEX:

One small, easy-to-swallow 20-mg tablet[†]

Indication	ACIPHEX Daily Dosage [‡]	Length of Therapy
Healing and symptomatic relief of erosive GERD		4 to 8 weeks [§]
Maintenance of healing of erosive GERD and reduction in relapse rates of erosive GERD heartburn symptoms	20 MG QD	As long as clinically indicated
Healing and symptomatic relief of duodenal ulcers		Up to 4 weeks [§]

[†]ACIPHEX tablets should be swallowed whole. They should not be chewed, crushed, or split.

[‡]A starting dose of 60 mg once daily is recommended for treatment of hypersecretory conditions, including Zollinger-Ellison syndrome (ZES).

[§]Additional courses of treatment may be considered if healing is incomplete.

^{||}Controlled studies extend to 52 weeks.

NEW

ONCE-A-DAY

AcipHex™
rabeprazole sodium
20-MG TABLETS

STRIKE BACK NOW

Before prescribing, please consult complete prescribing information of which the following is a brief summary.

INDICATIONS AND USAGE

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

ACIPHEX™ is indicated for short-term (4 to 8 weeks) treatment in the healing and symptomatic relief of erosive or ulcerative gastroesophageal reflux disease (GERD). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX™ may be considered.

Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

ACIPHEX™ is indicated for maintaining healing and reduction in relapse rates of heartburn symptoms in patients with erosive or ulcerative gastroesophageal reflux disease (GERD Maintenance).

Healing of Duodenal Ulcers

ACIPHEX™ is indicated for short-term (up to four weeks) treatment in the healing and symptomatic relief of duodenal ulcers. Most patients heal within four weeks.

Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome

ACIPHEX™ is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.

CONTRAINDICATIONS

Rabeprazole is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles or to any component of the formulation.

PRECAUTIONS

General

Symptomatic response to therapy with rabeprazole does not preclude the presence of gastric malignancy.

Patients with healed GERD were treated for up to 40 months with rabeprazole and monitored with serial gastric biopsies. Patients without *H. pylori* infection (221 of 326 patients) had no clinically important pathologic changes in the gastric mucosa. Patients with *H. pylori* infection at baseline (105 of 326 patients) had mild or moderate inflammation in the gastric body or mild inflammation in the gastric antrum. Patients with mild grades of infection or inflammation in the gastric body tended to change to moderate, whereas those graded moderate at baseline tended to remain stable. Patients with mild grades of infection or inflammation in the gastric antrum tended to remain stable. At baseline 8% of patients had atrophy of glands in the gastric body and 15% had atrophy in the gastric antrum. At endpoint, 15% of patients had atrophy of glands in the gastric body and 11% had atrophy in the gastric antrum. Approximately 4% of patients had intestinal metaplasia at some point during follow-up, but no consistent changes were seen.

Information for Patients

Patients should be cautioned that ACIPHEX™ delayed-release tablets should be swallowed whole. The tablets should not be chewed, crushed, or split.

Drug Interactions

Rabeprazole is metabolized by the cytochrome P450 (CYP450) drug metabolizing enzyme system. Studies in healthy subjects have shown that rabeprazole does not have clinically significant interactions with other drugs metabolized by the CYP450 system, such as warfarin and theophylline given as single oral doses, diazepam as a single intravenous dose, and phenytoin given as a single intravenous dose (with supplemental oral dosing). *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporine metabolism with an IC₅₀ of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days of dosing with 20 mg of rabeprazole. This degree of inhibition is similar to that by omeprazole at equivalent concentrations.

Rabeprazole produces sustained inhibition of gastric acid secretion. An interaction with compounds which are dependent on gastric pH for absorption may occur due to the magnitude of acid suppression observed with rabeprazole. For example, in normal subjects, coadministration of rabeprazole 20 mg QD resulted in an approximately 30% decrease in the bioavailability of ketoconazole and increases in the AUC and C_{max} for digoxin of 19% and 29%, respectively. Therefore, patients may need to be monitored when such drugs are taken concomitantly with rabeprazole. Co-administration of rabeprazole and antacids produced no clinically relevant changes in plasma rabeprazole concentrations.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 88/104-week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumor occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µg·hr/mL which is 1.6 times the human exposure (plasma AUC_{0-∞} = 0.88 µg·hr/mL) at the recommended dose for GERD (20 mg/day). In a 104-week carcinogenicity study in Sprague-Dawley rats, males were treated with oral doses of 5, 15, 30 and 60 mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumors in female rats in all doses including the lowest tested dose. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µg·hr/mL which is about 0.1 times the human exposure at the recommended dose for GERD. In male rats, no treatment related tumors were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µg·hr/mL (0.2 times the human exposure at the recommended dose for GERD).

Rabeprazole was positive in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward gene mutation test and the mouse lymphoma cell (L5178Y/TK+) forward gene mutation test. Its demethylated-metabolite was also positive in the Ames test. Rabeprazole was negative in the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test, and the *in vivo* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µg·hr/mL, about 10 times the human exposure at the recommended dose for GERD) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy

Teratogenic Effects. Pregnancy Category B: Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg·hr/mL, about 13 times the human exposure at the recommended dose for GERD) and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg·hr/mL, about 8 times the human exposure at the recommended dose for GERD) and have revealed no evidence of impaired fertility or harm to the fetus due to rabeprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Following intravenous administration of ¹⁴C-labeled rabeprazole to lactating rats, radioactivity in milk reached levels that were 2- to 7-fold higher than levels in the blood. It is not known if unmetabolized rabeprazole is excreted in human breast milk. Administration of rabeprazole to rats in late gestation and during lactation at doses of 400 mg/kg/day (about 195-times the human dose based on mg/m²) resulted in decreases in body weight gain of the pups. Since many drugs are excreted in milk, and because of the potential for adverse reactions to nursing infants from rabeprazole, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and efficacy of rabeprazole in pediatric patients has not been established.

Use in Women

Duodenal ulcer and erosive esophagitis healing rates in women are similar to those in men. Adverse events and laboratory test abnormalities in women occurred at rates similar to those in men.

Geriatric Use

Of the total number of subjects in clinical studies of ACIPHEX™, 19% were 65 years and over, while 4% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Worldwide, over 2900 patients have been treated with rabeprazole in Phase II-III clinical trials involving various dosages and durations of treatment. In general, rabeprazole treatment has been well-tolerated in both short-term and long-term trials. The adverse events rates were generally similar between the 10 and 20 mg doses.

Incidence in Controlled North American and European Clinical Trials

In an analysis of adverse events assessed as possibly or probably related to treatment appearing in greater than 1% of ACIPHEX™ patients and appearing with greater frequency than placebo in controlled North American and European trials, the incidence of headache was 2.4% (n=1552) for ACIPHEX™ versus 1.6% (n=258) for placebo.

In short and long-term studies, the following adverse events, regardless of causality, were reported in ACIPHEX™-treated patients. Rare events are those reported in <1/1000 patients.

Body as a Whole: asthenia, fever, allergic reaction, chills, malaise, chest pain substernal, neck rigidity, photosensitivity reaction, rare: abdominal engorged, face edema, hangover effect. **Cardiovascular System:** hypertension, myocardial infarct, electrocardiogram abnormal, migraine, syncope, angina pectoris, bundle branch block, palpitation, sinus bradycardia, tachycardia. Rare: bradycardia, pulmonary embolus, supraventricular tachycardia, thrombophlebitis, vasodilation, QTc prolongation and ventricular tachycardia. **Digestive System:** diarrhea, nausea, abdominal pain, vomiting, dyspepsia, flatulence, constipation, dry mouth, eructation, gastroenteritis, rectal hemorrhage, melena, anorexia, cholelithiasis, mouth ulceration, stomatitis, dysphagia, gingivitis, cholecystitis, increased appetite, abnormal stools, colitis, esophagitis, glossitis, pancreatitis, proctitis. Rare: bloody diarrhea, cholangitis, duodenitis, gastrointestinal hemorrhage, hepatic encephalopathy, hepatitis, hepatoma, liver fatty deposit, salivary gland enlargement, thirst. **Endocrine System:** hyperthyroidism, hypothyroidism. **Hemic & Lymphatic System:** anemia, ecchymosis, lymphadenopathy, hypochromic anemia. **Metabolic & Nutritional Disorders:** peripheral edema, edema, weight gain, gout, dehydration, weight loss. **Musculo-Skeletal System:** myalgia, arthritis, leg cramps, bone pain, arthrosis, bursitis. Rare: twitching. **Nervous System:** insomnia, anxiety, dizziness, depression, nervousness, somnolence, hypotonia, neuralgia, vertigo, convulsion, abnormal dreams, libido decreased, neuropathy, paresthesia, tremor. Rare: agitation, amnesia, confusion, extrapyramidal syndrome, hyperkinesia. **Respiratory System:** dyspnea, asthma, epistaxis, laryngitis, hiccup, hyperventilation. Rare: apnea, hypoxia. **Skin and Appendages:** rash, pruritis, sweating, urticaria, alopecia. Rare: dry skin, herpes zoster, psoriasis, skin discoloration. **Special Senses:** cataract, amblyopia, glaucoma, dry eyes, abnormal vision, tinnitus, otitis media. Rare: corneal opacity, blurry vision, diplopia, deafness, eye pain, retinal degeneration, strabismus. **Urogenital System:** cystitis, urinary frequency, dysmenorrhea, dysuria, kidney calculus, metrorrhagia, polyuria. Rare: breast enlargement, hematuria, leukorrhea, menorrhagia, orchitis, urinary incontinence.

Laboratory Values: The following changes in laboratory parameters were reported as adverse events: abnormal platelets, albuminuria, creatine phosphokinase increased, erythrocytes abnormal, hypercholesterolemia, hyperglycemia, hyperlipemia, hypokalemia, hyponatremia, leukocytosis, leukorrhea, liver function tests abnormal, prostatic specific antigen increase, SGPT increased, erythrocytes abnormal, WBC abnormal.

In controlled clinical studies, 3/1456 (0.2%) patients treated with rabeprazole and 2/237 (0.8%) patients treated with placebo developed treatment-emergent abnormalities (which were either new on study or present at study entry with an increase of 1.25 x baseline value) in SGOT (AST), SGPT (ALT), or both. None of the three rabeprazole patients experienced chills, fever, right upper quadrant pain, nausea or jaundice.

Post-marketing Adverse Events: Additional adverse events reported from worldwide marketing experience with rabeprazole sodium are: sudden death, coma and hyperammonemia, jaundice, rhabdomyolysis, disorientation and delirium, bullous and other drug eruptions of the skin, interstitial pneumonia, and TSH elevations. In most instances, the relationship to rabeprazole sodium was unclear. In addition, agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, and thrombocytopenia have been reported.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug. There has been no experience with large overdoses with rabeprazole. Seven reports of accidental overdose with rabeprazole have been received. The maximum reported overdose was 80 mg. There were no clinical signs or symptoms associated with any reported overdose. Patients with Zollinger-Ellison syndrome have been treated with up to 120 mg rabeprazole QD. No specific antidote for rabeprazole is known. Rabeprazole is extensively protein bound and is not readily dialyzable. In the event of overdose, treatment should be symptomatic and supportive. Single oral doses of rabeprazole at 786 mg/kg and 1024 mg/kg were lethal to mice and rats, respectively. The single oral dose of 2000 mg/kg was not lethal to dogs. The major symptoms of acute toxicity were hypoxia, labored respiration, lateral or prone position and convulsion in mice and rats and watery diarrhea, tremor, convulsion and coma in dogs.

DOSAGE AND ADMINISTRATION

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

The recommended adult oral dose is one ACIPHEX™ 20 mg delayed-release tablet to be taken once daily for four to eight weeks. (See INDICATIONS AND USAGE). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX™ may be considered.

Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD Maintenance)

The recommended adult oral dose is one ACIPHEX™ 20 mg delayed-release tablet to be taken once daily. (See INDICATIONS AND USAGE).

Healing of Duodenal Ulcers

The recommended adult oral dose is one ACIPHEX™ 20 mg delayed-release tablet to be taken once daily after the morning meal for a period up to four weeks. (See INDICATIONS AND USAGE). Most patients with duodenal ulcer heal within four weeks. A few patients may require additional therapy to achieve healing.

Treatment of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

The dosage of ACIPHEX™ in patients with pathologic hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Some patients may require divided doses. Doses up to 100 mg QD and 60 mg BID have been administered. Some patients with Zollinger-Ellison syndrome have been treated continuously with ACIPHEX™ for up to one year.

No dosage adjustment is necessary in elderly patients, in patients with renal disease or in patients with mild to moderate hepatic impairment. Administration of rabeprazole to patients with mild to moderate liver impairment resulted in increased exposure and decreased elimination. Due to the lack of clinical data on rabeprazole in patients with severe hepatic impairment, caution should be exercised in those patients.

ACIPHEX™ tablets should be swallowed whole. The tablets should not be chewed, crushed, or split.



Manufactured by Eisai Co., Ltd., Misato, Japan

Made in Japan

Marketed by



Marketed by



Teaneck, NJ 07666

Titusville, NJ 08560-0200

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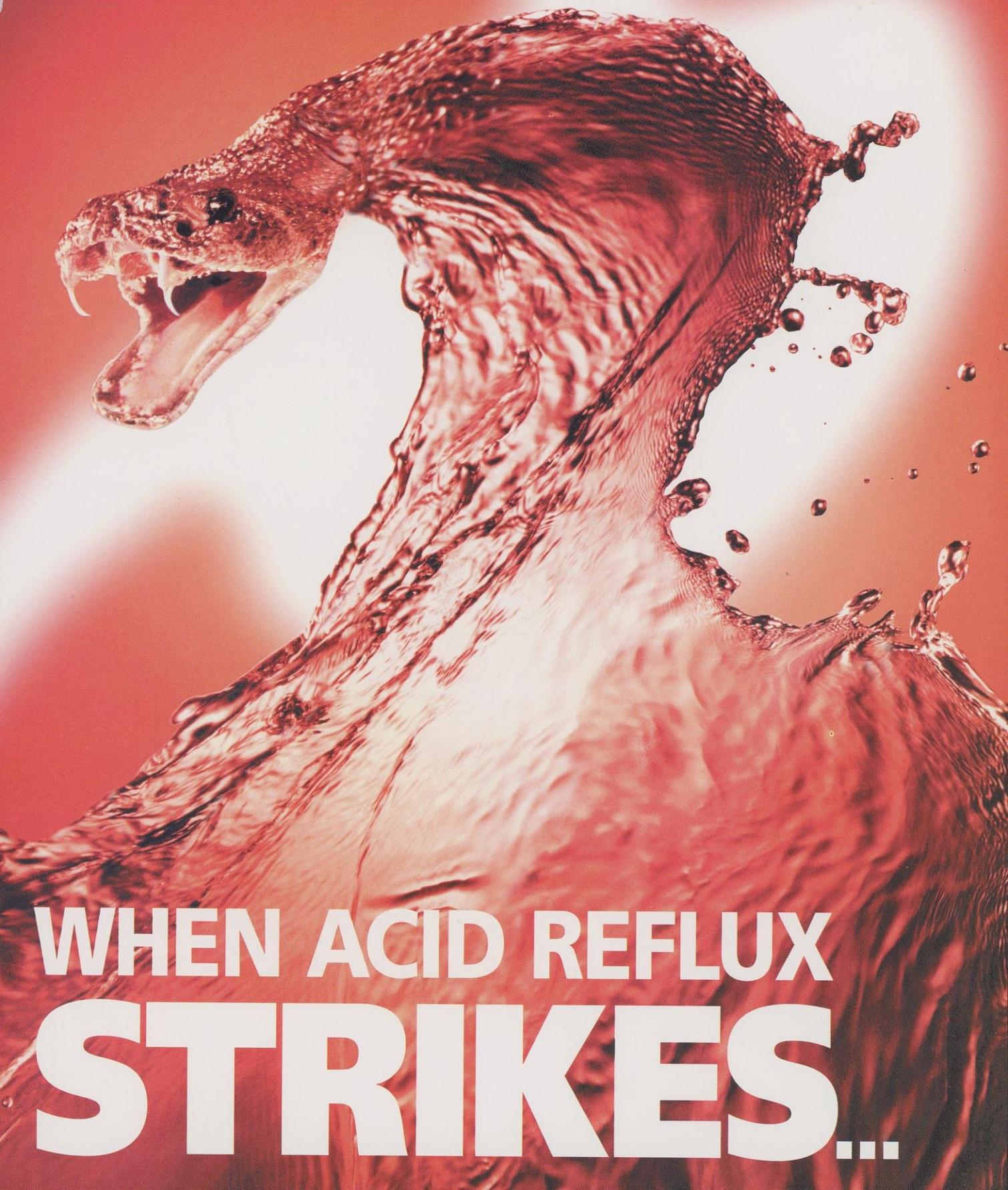
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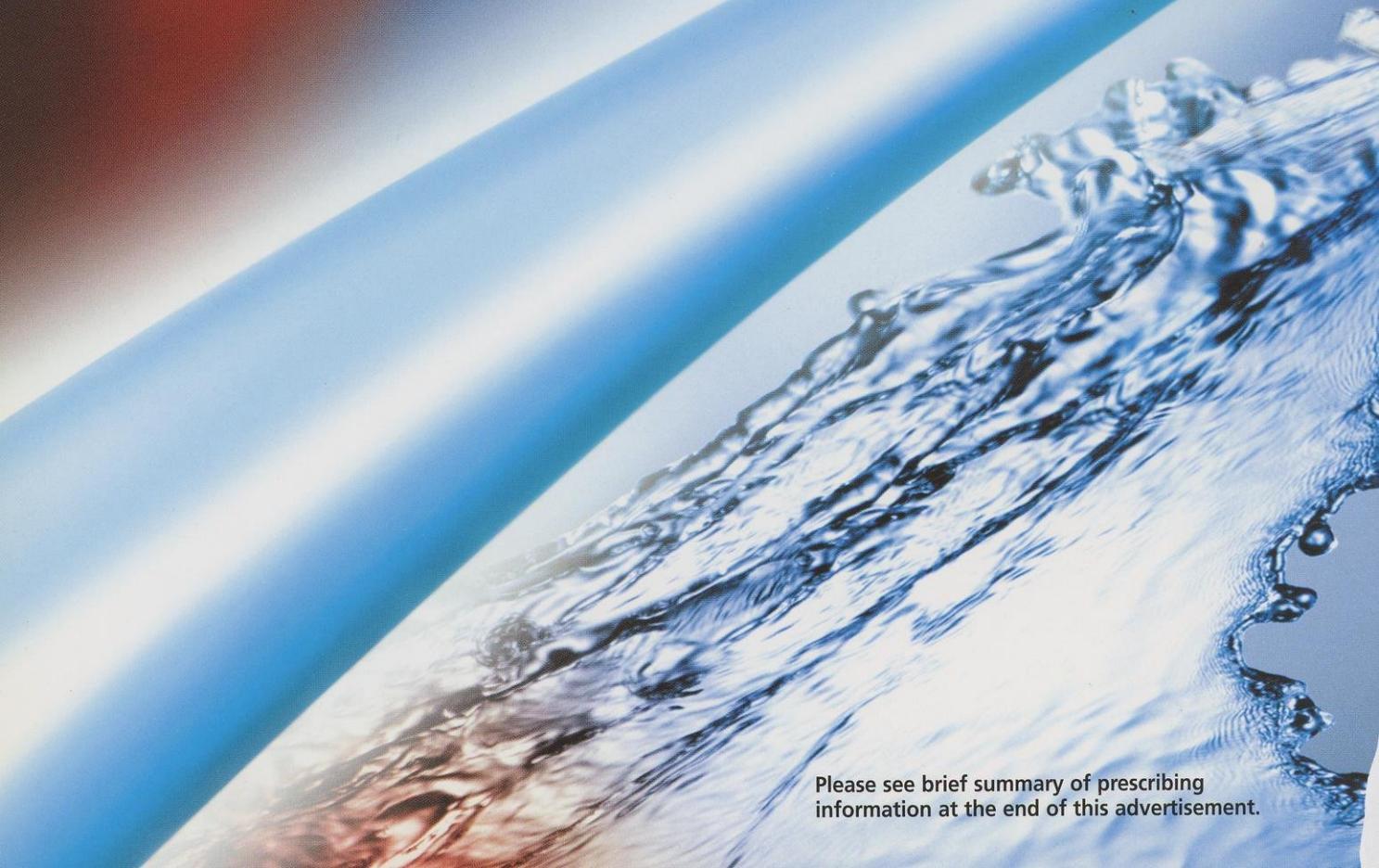
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NEW IN ACID SUPPRESSION
FOR EROSION GERD



**WHEN ACID REFLUX
STRIKES...**

STRIKE



Please see brief summary of prescribing
information at the end of this advertisement.

BACK WITH NEW

ONCE-A-DAY

AcipHex™

rabeprazole sodium

20-MG TABLETS

A new proton pump inhibitor with proven acid suppression for:

- Healing and symptomatic relief of erosive GERD
- Maintenance of healed erosive GERD
- Reduction in relapse rates of erosive GERD heartburn symptoms
- Healing and symptomatic relief of duodenal ulcers
- Treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome (ZES)

STRIKE BACK NOW

NEW

ACIPHEX™: CONSISTENT MAINTENANCE OF LONG-TERM HEALING IN EROSIONAL GERD

ACIPHEX:
Endoscopically proven to maintain healing for 52 weeks



Taken from 2 US, 52-week, multicenter, double-blind, randomized, multiple-dose, placebo-controlled studies of patients with healed ulcerative or erosive GERD (N=488)

Continued relief of major erosive GERD symptoms for 52 weeks

Percent of patients without relapse in:

Daytime heartburn	94% to 97%
Nighttime heartburn	91% to 98%

Please see brief summary of prescribing information at the end of this advertisement.

IN EROSIONAL GERD

HIT HEARTBURN HARD



ACIPHEX®—24-hour acid control
from the first dose

- Symptom relief on day 1*¹
- All-day, all-night acid control²
- An excellent safety profile

In clinical trials the most common side effect assessed as possibly related to ACIPHEX was headache (2.4% vs 1.6% for placebo).

Symptomatic response to therapy does not preclude the presence of gastric malignancy. ACIPHEX is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles, or to any component of the formulation.

ONCE-A-DAY

AcipHex®
rabeprazole sodium
20-MG TABLETS

*Erosive GERD patients with moderate to severe symptoms at baseline who achieved mild or no symptoms during treatment in a large, open-label, multicenter study (n=1449 daytime; n=1469 nighttime).

Please see brief summary of prescribing information on adjacent page.

24-hour acid control from the first dose

Before prescribing, please consult complete prescribing information of which the following is a brief summary.

INDICATIONS AND USAGE

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

ACIPHEX® is indicated for short-term (4 to 8 weeks) treatment in the healing and symptomatic relief of erosive or ulcerative gastroesophageal reflux disease (GERD). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX® may be considered.

Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

ACIPHEX® is indicated for maintaining healing and reduction in relapse rates of heartburn symptoms in patients with erosive or ulcerative gastroesophageal reflux disease (GERD Maintenance).

Healing of Duodenal Ulcers

ACIPHEX® is indicated for short-term (up to four weeks) treatment in the healing and symptomatic relief of duodenal ulcers. Most patients heal within four weeks.

Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome

ACIPHEX® is indicated for the long-term treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome.

CONTRAINDICATIONS

Rabeprazole is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles or to any component of the formulation.

PRECAUTIONS

General

Symptomatic response to therapy with rabeprazole does not preclude the presence of gastric malignancy.

Patients with healed GERD were treated for up to 40 months with rabeprazole and monitored with serial gastric biopsies. Patients without *H. pylori* infection (221 of 326 patients) had no clinically important pathologic changes in the gastric mucosa. Patients with *H. pylori* infection at baseline (105 of 326 patients) had mild or moderate inflammation in the gastric body or mild inflammation in the gastric antrum. Patients with mild grades of infection or inflammation in the gastric body tended to change to moderate, whereas those graded moderate at baseline tended to remain stable. Patients with mild grades of infection or inflammation in the gastric antrum tended to remain stable. At baseline 8% of patients had atrophy of glands in the gastric body and 15% had atrophy in the gastric antrum. At endpoint, 15% of patients had atrophy of glands in the gastric body and 11% had atrophy in the gastric antrum. Approximately 4% of patients had intestinal metaplasia at some point during follow-up, but no consistent changes were seen.

Information for Patients

Patients should be cautioned that ACIPHEX® delayed-release tablets should be swallowed whole. The tablets should not be chewed, crushed, or split.

Drug Interactions

Rabeprazole is metabolized by the cytochrome P450 (CYP450) drug metabolizing enzyme system. Studies in healthy subjects have shown that rabeprazole does not have clinically significant interactions with other drugs metabolized by the CYP450 system, such as warfarin and theophylline given as single oral doses, diazepam as a single intravenous dose, and phenytoin given as a single intravenous dose (with supplemental oral dosing). *In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporine metabolism with an IC_{50} of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days of dosing with 20 mg of rabeprazole. This degree of inhibition is similar to that by omeprazole at equivalent concentrations.

Rabeprazole produces sustained inhibition of gastric acid secretion. An interaction with compounds which are dependent on gastric pH for absorption may occur due to the magnitude of acid suppression observed with rabeprazole. For example, in normal subjects, co-administration of rabeprazole 20 mg QD resulted in an approximately 30% decrease in the bioavailability of ketoconazole and increases in the AUC and V_{max} for digoxin of 19% and 29%, respectively. Therefore, patients may need to be monitored when such drugs are taken concomitantly with rabeprazole. Co-administration of rabeprazole and antacids produced no clinically relevant changes in plasma rabeprazole concentrations.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 88/104-week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumor occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 $\mu\text{g}\cdot\text{hr}/\text{mL}$ which is 1.6 times the human exposure (plasma $AUC_{0-\infty} = 0.88 \mu\text{g}\cdot\text{hr}/\text{mL}$) at the recommended dose for GERD (20 mg/day). In a 104-week carcinogenicity study in Sprague-Dawley rats, males were treated with oral doses of 5, 15, 30, and 60 mg/kg/day and females with 5, 15, 30, 60, and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumors in female rats at all doses including the lowest tested dose. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 $\mu\text{g}\cdot\text{hr}/\text{mL}$ which is about 0.1 times the human exposure at the recommended dose for GERD. In male rats, no treatment related tumors were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 $\mu\text{g}\cdot\text{hr}/\text{mL}$ (0.2 times the human exposure at the recommended dose for GERD).

Rabeprazole was positive in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward gene mutation test and the mouse lymphoma cell (L5178Y/TK+) forward gene mutation test. Its demethylated-metabolite was also positive in the Ames test. Rabeprazole was negative in the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test, and the *in vivo* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 $\mu\text{g}\cdot\text{hr}/\text{mL}$, about 10 times the human exposure at the recommended dose for GERD) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy

Teratogenic Effects. Pregnancy Category B: Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 $\mu\text{g}\cdot\text{hr}/\text{mL}$, about 13 times the human exposure at the recommended dose for GERD) and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 $\mu\text{g}\cdot\text{hr}/\text{mL}$, about 8 times the human exposure at the recommended dose for GERD) and have revealed no evidence of impaired fertility or harm to the fetus due to rabeprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Following intravenous administration of ^{14}C -labeled rabeprazole to lactating rats, radioactivity in milk reached levels that were 2- to 7-fold higher than levels in the blood. It is not known if unmetabolized rabeprazole is excreted in human breast milk. Administration of rabeprazole to rats in late gestation and during lactation at doses of 400 mg/kg/day (about 195-times the human dose based on mg/m^2) resulted in decreases in body weight gain of the pups. Since many drugs are excreted in milk, and because of the potential for adverse reactions to nursing infants from rabeprazole, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of rabeprazole in pediatric patients have not been established.

References:

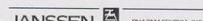
1. Data on file, Eisai Inc.
2. Pantoflickova D, Dorta G, Jornod P, et al. Identification of the characteristics influencing the degree of antisecretory activity of PPIs [abstract]. *Gastroenterology*. 2000;118:A5895.

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Use in Women

Duodenal ulcer and erosive esophagitis healing rates in women are similar to those in men. Adverse events and laboratory test abnormalities in women occurred at rates similar to those in men.

Geriatric Use

Of the total number of subjects in clinical studies of ACIPHEX®, 19% were 65 years and over, while 4% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Worldwide, over 2900 patients have been treated with rabeprazole in Phase II-III clinical trials involving various dosages and durations of treatment. In general, rabeprazole treatment has been well-tolerated in both short-term and long-term trials. The adverse events rates were generally similar between the 10 and 20 mg doses.

Incidence in Controlled North American and European Clinical Trials

In an analysis of adverse events assessed as possibly or probably related to treatment appearing in greater than 1% of ACIPHEX® patients and appearing with greater frequency than placebo in controlled North American and European trials, the incidence of headache was 2.4% (n=152) for ACIPHEX® versus 1.6% (n=258) for placebo. In short and long-term studies, the following adverse events, regardless of causality, were reported in ACIPHEX®-treated patients. Rare events are those reported in ≤ 1 patient.

Body as a Whole: asthenia, fever, allergic reaction, chills, malaise, chest pain substernal, neck rigidity, photosensitivity reaction. **Rare:** abdomen enlarged, face edema, hangover effect. **Cardiovascular System:** hypertension, myocardial infarct, electrocardiogram abnormal, migraine, syncope, angina pectoris, bundle branch block, palpitation, sinus bradycardia, tachycardia. **Rare:** bradycardia, pulmonary embolus, supraventricular tachycardia, thrombophlebitis, vasodilation, QTc prolongation and ventricular tachycardia. **Digestive System:** diarrhea, nausea, abdominal pain, vomiting, dyspepsia, flatulence, constipation, dry mouth, eructation, gastroenteritis, rectal hemorrhage, melena, anorexia, cholelithiasis, mouth ulceration, stomatitis, dysphagia, gingivitis, cholecystitis, increased appetite, abnormal stools, colitis, esophagitis, glossitis, pancreatitis, proctitis. **Rare:** bloody diarrhea, cholangitis, duodenitis, gastrointestinal hemorrhage, hepatic encephalopathy, hepatitis, hepatoma, liver fatty deposit, salivary gland enlargement, thirst. **Endocrine System:** hyperthyroidism, hypothyroidism. **Hemic & Lymphatic System:** anemia. **Metabolic & Nutritional Disorders:** peripheral edema, edema, weight gain, gout, dehydration, weight loss. **Musculo-Skeletal System:** myalgia, arthritis, leg cramps, bone pain, arthrosis, bursitis. **Rare:** twitching. **Nervous System:** insomnia, anxiety, dizziness, depression, nervousness, somnolence, hypertension, neuralgia, vertigo, convulsion, abnormal dreams, libido decreased, neuropathy, paresthesia, tremor. **Rare:** agitation, amnesia, confusion, extrapyramidal syndrome, hyperkinesia. **Respiratory System:** dyspnea, asthma, epistaxis, laryngitis, hiccup, hyperventilation. **Rare:** apnea, hypoventilation. **Skin and Appendages:** rash, pruritus, sweating, urticaria, alopecia. **Rare:** dry skin, herpes zoster, psoriasis, skin, discoloration. **Special Senses:** cataract, amblyopia, glaucoma, dry eyes, abnormal vision, tinnitus, otitis media. **Rare:** corneal opacity, blurry vision, diplopia, deafness, eye pain, retinal degeneration, strabismus. **Urogenital System:** cystitis, urinary frequency, dysmenorrhea, dysuria, kidney calculus, metrorrhagia, polycystitis. **Rare:** breast enlargement, hematuria, impotence, leukorrhea, menorrhagia, orchitis, urinary incontinence.

Laboratory Values: The following changes in laboratory parameters were reported as adverse events: abnormal platelets, albuminuria, creatine phosphokinase increased, erythrocytes abnormal, hypercholesterolemia, hyperglycemia, hyperlipemia, hypokalemia, hyponatremia, leukocytosis, leukorrhea, liver function tests abnormal, prostaglandin specific antigen increase, SGPT increased, urine abnormality, WBC abnormal.

In controlled clinical studies, 3/1456 (0.2%) patients treated with rabeprazole and 2/237 (0.8%) patients treated with placebo developed treatment-emergent abnormalities (which were either new on study or present at study entry with an increase of 1.25 x baseline value) in SGOT (AST), SGPT (ALT), or both. None of the three rabeprazole patients experienced chills, fever, right upper quadrant pain, nausea or diarrhea.

Post-Marketing Adverse Events: Additional adverse events reported from worldwide marketing experience with rabeprazole sodium are: sudden death, coma and hyperammonemia, jaundice, rhabdomyolysis, disorientation and delirium, anaphylaxis, angioedema, bullous and other drug eruptions of the skin, interstitial pneumonia, and TSH elevations. In most instances, the relationship to rabeprazole sodium was unclear. In addition, agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, and thrombocytopenia have been reported.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug. There has been no experience with large overdoses with rabeprazole. Seven reports of accidental overdose with rabeprazole have been received. The maximum reported overdose was 80 mg. There were no clinical signs or symptoms associated with any reported overdose. Patients with Zollinger-Ellison syndrome have been treated with up to 120 mg rabeprazole QD. No specific antidote for rabeprazole is known. Rabeprazole is extensively protein bound and is not readily dialyzable. In the event of overdose, treatment should be symptomatic and supportive. Single oral doses of rabeprazole at 786 mg/kg and 1024 mg/kg were lethal to mice and rats, respectively. The single oral dose of 2000 mg/kg was not lethal to dogs. The major symptoms of acute toxicity were hypoactivity, labored respiration, lateral or prone position and convulsion in mice and rats and watery diarrhea, tremor, convolution and coma in dogs.

DOSE AND ADMINISTRATION

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily for four to eight weeks. (See INDICATIONS AND USAGE). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX® may be considered.

Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD Maintenance)

The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily. (See INDICATIONS AND USAGE).

Healing of Duodenal Ulcers

The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily after the morning meal for a period up to four weeks. (See INDICATIONS AND USAGE). Most patients with duodenal ulcer heal within four weeks. A few patients may require additional therapy to achieve healing.

Treatment of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

The dosage of ACIPHEX® in patients with pathologic hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Some patients may require divided doses. Doses up to 100 mg QD and 60 mg BID have been administered. Some patients with Zollinger-Ellison syndrome have been treated continuously with ACIPHEX® for up to one year.

No dosage adjustment is necessary in elderly patients, in patients with renal disease or in patients with mild to moderate hepatic impairment. Administration of rabeprazole to patients with mild to moderate liver impairment resulted in increased exposure and decreased elimination. Due to the lack of clinical data on rabeprazole in patients with severe hepatic impairment, caution should be exercised in those patients.

ACIPHEX® tablets should be swallowed whole. The tablets should not be chewed, crushed, or split.

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