ACIPHEX® 200186
(a-ss-uh-lek-sens)
(rabeprazole sodium)
Delayed-Release Tablets

DESCRIPTION
The active ingredient in ACIPHEX® Delayed-Release Tablets is rabeprazole sodium, a substituted benzimidazole that inhibits gastric acid secretion. Rabeprazole sodium is known chemically as 2-[[4-[2-[[(2-R)-2-hydroxyethyl]-methyl]amino]-ethyl]-methylsulfanyl]-4-methyl-1H-benzimidazole sodium salt. It has an empirical formula of C_{18}H_{24}N_{4}O_{2}S and a molecular weight of 381.43. Rabeprazole sodium is a white to slightly yellowish-white solid. It is very soluble in water and methanol, freely soluble in ethanol, chloroform, and benzene, but insoluble in ether and n-hexane. The stability of rabeprazole sodium is a function of pH; it is rapidly degraded in acid media, and is more stable under alkaline conditions. The structural formula is:

ACIPHEX® is available for oral administration as delayed-release, enteric-coated tablets containing 20 mg of rabeprazole sodium. Inactive ingredients are calcium, hydroxypropyl cellulose, magnesium oxide, low-substituted hydroxypropyl cellulose, magnesium stearate, other cellulose, hydroxypropyl methylcellulose phthalate, disodium edetate, sodium, and ferric oxide (yellow) as a coloring agent.

CLINICAL PHARMACOLOGY
Pharmacokinetics and Metabolism
ACIPHEX® delayed-release tablets are enteric-coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach relatively intact. After oral administration of 20 mg of ACIPHEX®, peak plasma concentrations (C_max) of rabeprazole occur over a range of 2.0 to 5.0 hours (Tmax). The plasma concentration of C_max and AUC are linear over an oral dose range of 10 mg to 40 mg. There is no appreciable accumulation when doses of 10 mg to 40 mg are administered every 24 hours; the pharmacokinetics of rabeprazole are not altered by multiple dosing. The plasma half-life ranges from 1.8 to 2 hours.

Absorption: Following oral administration of 20 mg, rabeprazole is absorbed and can be detected in plasma by 1 hour. Absolute bioavailability for a 20 mg oral tablet of rabeprazole (compared to intravenous administration) is approximately 52%.

The effects of food on the absorption of rabeprazole have not been evaluated.

Distribution: Rabeprazole is 96.3% bound to human plasma proteins.

Metabolism: Rabeprazole is extensively metabolized. The thiol and sulphone are the primary metabolites measured in human plasma. These metabolites were not observed to have significant antrectomy activity. In vivo studies have demonstrated that rabeprazole is primarily metabolized in the liver by cytochrome P450 2A4 (sulphone metabolism) and CYP2C9 (desmethyl rabeprazole). The thiol metabolite is formed by reduction of rabeprazole.

Elimination: Following a single 20 mg oral dose of 14C-labeled rabeprazole, approximately 90% of the drug was eliminated in the urine, primarily as the sulphone and mercapturic acid metabolites. The remainder of the dose was recovered in the feces. Total recovery of radioactivity was 99.8%. No unchanged rabeprazole was recovered in the urine or feces.

Special Populations
Geriatric: In 20 healthy elderly subjects administered 20 mg rabeprazole once daily for seven days, AUC values approximately doubled and the C_max increased by 89% compared to values in a parallel younger control group. There was no evidence of drug accumulation after once daily administration. (See PRECAUTIONS.)

Pediatric: The pharmacokinetics of rabeprazole in pediatric patients under the age of 18 years have not been studied.

Gender and Race: In analyses adjusted for body mass and height, rabeprazole pharmacokinetics showed no clinically significant differences between male and female subjects. In studies that used different cut points for rabeprazole, AUC_{24h} values for healthy Japanese men were approximately 50-60% greater than values derived from pooled data from healthy men in the United States.

Renal Disease: In 10 patients with stable end-stage renal disease requiring maintenance hemodialysis (creatinine clearance ≤ 15 ml/min/1.73 m²), no clinically significant differences were observed in the pharmacokinetics of rabeprazole after a single 20 mg oral dose when compared to 10 healthy volunteers.

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC_{24h} was approximately doubled, the elimination half-life was 2 to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In multiple dose studies of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, AUC_{24h} and C_max values increased approximately 20% compared to values in healthy age- and gender-matched subjects. These changes were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to the DOSAGE AND ADMINISTRATION section for information on dosage adjustment in patients with hepatic impairment.

PHARMACODYNAMICS
Mechanism of Action
Rabeprazole belongs to a class of antistomacy compounds (substituted benzimidazole proton-pump inhibitors) that do not exhibit anticholinergic or histamine H2-receptor antagonist properties, but suppress gastric acid secretion by inhibiting the gastric H+/K-ATPase at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, the enzyme has been characterized as a gastric proton-pump inhibitor. Rabeprazole blocks the final step of gastric acid secretion.

In gastric parietal cells, rabeprazole is protonated, accumulates, and is transformed to an active sulfenamide. When studied in vitro, rabeprazole is chemically activated at pH 1.2 with a half-life of 78 seconds. It inhibits acid transport in porcine gastric vesicles with a half-life of 90 seconds.

Anti-Secretory Activity
The anti-secretory effect begins within one hour after oral administration of 20 mg of ACIPHEX®. The median inhibitory effect of ACIPHEX® on 24-hour gastric acidity is 88% at maximal within the first dose. ACIPHEX® 20 mg inhibits basal and pentagastrin-stimulated acid secretion versus placebo by 80% and 90%, respectively, and increases the percent of a 24-hour period that the gastric pH-3 from 10% to 60% (see table below). This relatively prolonged pharmacodynamic action compared to the short pharmokinetic half-life (1-2 hours) reflects the sustained inactivation of the H+/K-ATPase.

Gastric Acid Parameters
ACIPHEX® Versus Placebo After 7 Days of Daily Dosing

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ACIPHEX® 20 mg OD</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal Acid Output (mmol/hr)</td>
<td>0.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Stimulated Acid Output (mmol/hr)</td>
<td>0.6*</td>
<td>13.3</td>
</tr>
<tr>
<td>% Time Gastric pH-3</td>
<td>95*</td>
<td>10</td>
</tr>
</tbody>
</table>

*p <0.01 versus placebo

Compared to placebo, ACIPHEX®, 10 mg, 20 mg, and 40 mg, administered once daily for 7 days significantly decreased intragastric acidity with all doses for each of four meal-related intervals and the 24-hour time period overall. In this study, there were no statistically significant differences between doses; however, there was a significant dose-related decrease in intragastric acidity. The ability of rabeprazole to cause a dose-related decrease in mean intragastric acidity is illustrated below.
AUC Acidity (mean±SD)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>10 mg REP (N=26)</th>
<th>20 mg REP (N=26)</th>
<th>40 mg REP (N=26)</th>
<th>Placebo (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:00 – 13:00</td>
<td>16.3±13.2*</td>
<td>12.9±14.2*</td>
<td>7.9±14.7*</td>
<td>91.1±59.7</td>
</tr>
<tr>
<td>12:00 – 18:00</td>
<td>5.9±5.9*</td>
<td>8.3±9.6*</td>
<td>1.5±5.6*</td>
<td>95.5±45.7</td>
</tr>
<tr>
<td>19:00 – 08:00</td>
<td>0.1±1.0*</td>
<td>0.1±0.6*</td>
<td>0.0±0.2*</td>
<td>11.9±15.0</td>
</tr>
<tr>
<td>AUC 24 hours</td>
<td>129±4.5*</td>
<td>106±6.7*</td>
<td>7.6±5.8*</td>
<td>47.9±16.5</td>
</tr>
</tbody>
</table>

(*p<0.001 versus placebo)

After administration of 20 mg ACPH/P in daily doses for eight days, the mean percent of time that gastric pH was ≥ 4 was significantly greater than placebo (see table below). The decrease in gastric acidity and the increase in gastric pH observed with 20 mg ACPH/P administered once daily for eight days were compared to the same parameters for placebo, as illustrated below.

**Gastric Acid Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ACPH/P 20 mg OD</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Day 8</td>
<td>Day 1</td>
</tr>
<tr>
<td>Mean Gastric Acidity (mEq/L)</td>
<td>34±3.8</td>
<td>17±0.8</td>
</tr>
<tr>
<td>Median trough pH (24-hr)</td>
<td>3.7±3</td>
<td>3.3±1</td>
</tr>
<tr>
<td>% Time Gastric pH ≥ 4</td>
<td>54±2</td>
<td>68±2</td>
</tr>
<tr>
<td>% Time Gastric pH &lt; 4</td>
<td>46±1</td>
<td>32±1</td>
</tr>
</tbody>
</table>

(*p<0.001 versus placebo)

**Effects on Esophageal Acid Exposure**

In patients with gastroesophageal reflux disease (GERD) and moderate to severe esophageal acid exposure, ACPH/P 20 mg and 40 mg per day decreased 24-hour esophageal acid exposure. After seven days of treatment, the percentage of time that esophageal pH was ≥4 decreased from baselines of 34% for 20 mg and 33% for 40 mg to 5% and 1%, respectively. Normalization of 24-hour intragastric acid exposure was correlated to gastric pH for at least 25% of the 24-hour period; this level was achieved in 96% of subjects receiving ACPH/P 20 mg and in 100% of subjects receiving ACPH/P 40 mg. With ACPH/P 20 mg and 40 mg per day, effects on gastric and esophageal pH were significant and substantial after one day of treatment, and more pronounced after seven days of treatment.

**Effects on Serum Gastrin**

In patients given daily doses of ACPH/P for up to eight weeks to treat ulcerative or erosive esophagitis and in patients treated for up to 52 weeks to prevent recurrence of disease, the median fasting gastrin level increased in a dose-related manner. The group median values stayed within the normal range.

**Effects on Enterochromaffin-like (ECL) Cells**

Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially in females (see Carcinogenesis, Mutagenesis, Impairment of fertility).

In over 400 patients treated with ACPH/P (10 or 20 mg/day) for up to one year, there was no increase in ECL cell hyperplasia compared to control patients with time and dose, which is consistent with the pharmacological action of the proton-pump inhibitor. No patient developed the adenomatous, dysplastic, or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumors observed in rats.

**Endocrine Effects**

Studies in humans for up to one year have not revealed clinically significant effects on the endocrine system. In healthy male volunteers treated with ACPH/P for 13 days, no clinically relevant changes were detected in the following endocrine parameters evaluated: T3, T4, TSH, prolactin, thyrotropin-releasing hormone, triiodothyronine, thyroxine, thyrotropin-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, folate-stimulating hormone, lutropin, luteinizing hormone, follicle-stimulating hormone, prolactin, somatostatin, cortisol, and urinary 8-hydroxydeoxyguanosine, serotonin, somatostatin, and cecum and rectal flora.

Other Effects

In humans treated with ACPH/P for up to one year, no systemic effects have been observed on the central nervous, lymphoid, hematopoietic, renal, hepatic, cardiovascular, or respiratory systems. No data are available on long-term treatment with ACPH/P and ocular effects.

**CLINICAL STUDIES**

**Healing of Esophagitis or Ulcerative Gastroesophageal Reflux Disease (GERD)**

In a U.S., multicenter, randomized, double-blind, placebo-controlled study, 103 patients were treated for up to eight weeks with placebo, 10 mg, 20 mg or 40 mg ACPH/P OD. For this and all studies of GERD healing, only patients with GERD symptoms and at least grade 2 erosions (modified Ottawa grading scale) were eligible for entry. Endoscopic healing was defined as grade 0 or 1. Each naphthoquinone dose was significantly superior to placebo in producing endoscopic healing after four and eight weeks of treatment. The percentage of patients demonstrating endoscopic healing was as follows:

<table>
<thead>
<tr>
<th>Week</th>
<th>ACPH/P 20 mg OD</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>63%*</td>
<td>36%</td>
</tr>
<tr>
<td>8</td>
<td>93%*</td>
<td>36%</td>
</tr>
</tbody>
</table>

(*p<0.001 versus placebo)

**Healing of Esophagitis or Ulcerative Gastroesophageal Reflux Disease (GERD) Percentage of Patients Healed**

<table>
<thead>
<tr>
<th>Week</th>
<th>ACPH/P 20 mg OD</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>59%*</td>
<td>36%</td>
</tr>
<tr>
<td>8</td>
<td>87%*</td>
<td>66%</td>
</tr>
</tbody>
</table>

(*p<0.001 versus placebo)

ACPH/P 20 mg OD was significantly more effective than naphthoquinone 10 mg OD in the percentage of patients with complete resolution of heartburn at Weeks 4 and 8 (p<0.001). ACPH/P 20 mg OD once daily was also more effective in complete resolution of daytime heartburn (p=0.025), and nighttime heartburn (p=0.012) at both Weeks 4 and 8, with significant differences by the end of the first week at the study.

**Long-term Maintenance of Healing of Esophagitis or Ulcerative Gastroesophageal Reflux Disease (GERD Maintenance)**

The long-term maintenance of healing in patients with erosive esophagitis previously healed with endoscopic treatment therapy was assessed in two U.S., multicenter, randomized, double-blind, placebo-controlled studies of identical design of 52 weeks duration. The two studies compared 229 and 255 patients, respectively, to receive either 10 mg or 20 mg ACPH/P OD or placebo. As demonstrated in the tables below, ACPH/P was significantly superior to placebo in both studies with respect to the maintenance of healing of GERD and the proportions of patients remaining free of heartburn symptoms at 52 weeks.
LONG-TERM MAINTENANCE OF HEALING OF EROSION OR ULCERATIVE GASTROESOPHAGEAL REFLUX DISEASE (GERD) MAINTENANCE

PERCENT OF PATIENTS IN ENDOSCOPIC REMISSION

<table>
<thead>
<tr>
<th>Study 1</th>
<th>ACIPHEX® 10 mg</th>
<th>ACIPHEX® 20 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>82%*</td>
<td>96%*</td>
<td>91%*</td>
</tr>
<tr>
<td>Week 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 52</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Placebo)

(0.001 versus placebo)

CLINICAL STUDIES (continued)

LONG-TERM MAINTENANCE OF HEALING OF EROSION OR ULCERATIVE GASTROESOPHAGEAL REFLUX DISEASE (GERD) MAINTENANCE

PERCENT OF PATIENTS WITHOUT RESPONSES IN HEARTBURN FREQUENCY AND DAYTIME AND NIGHTTIME HEARTBURN SEVERITY AT WEEK 52

<table>
<thead>
<tr>
<th>ACIPHEX® 10 mg</th>
<th>ACIPHEX® 20 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>46/55 (84%)*</td>
<td>48/52 (92%)*</td>
</tr>
<tr>
<td>Study 2</td>
<td>50/72 (69%)*</td>
<td>57/72 (79%)*</td>
</tr>
</tbody>
</table>

(Placebo)

(0.001 versus placebo)

HEALING OF DUODENAL ULCERS

In a U.S., randomized, double-blind, multi-center study assessing the effectiveness of 20 mg and 40 mg of ACIPHEX® QD versus placebo for healing endoscopically defined duodenal ulcers, 100 patients were treated for up to four weeks. ACIPHEX® was significantly superior to placebo in producing healing of duodenal ulcers. The percentages of patients with endoscopic healing are presented below:

<table>
<thead>
<tr>
<th>Week</th>
<th>ACIPHEX® 20 mg OD N=34</th>
<th>ACIPHEX® 40 mg OD N=33</th>
<th>Placebo N=33</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>44%</td>
<td>42%</td>
<td>21%</td>
</tr>
<tr>
<td>4</td>
<td>70%</td>
<td>91%*</td>
<td>39%</td>
</tr>
</tbody>
</table>

(Placebo)

(0.001 versus placebo)

(Placebo)

(0.001 versus placebo)

ACIPHEX® and omeprazole were comparable in providing complete resolution of symptoms.

PATHOLOGICAL HYPERSECRETORY CONDITIONS INCLUDING ZOLLINGER-ELLISON SYNDROME

Twelve patients with idiopathic gastritis or Zollinger-Ellison syndrome have been treated successfully with ACIPHEX® at doses from 30 to 120 mg for up to 12 months. ACIPHEX® produced satisfactory inhibition of gastric acid secretion in all patients and complete resolution of signs and symptoms of acid-peptic disease in all patients. The high doses of ACIPHEX® used to treat these patients with idiopathic gastritis were not associated with drug-related adverse effects.

INDICATIONS AND USAGE

HEALING OF EROSION OR ULCERATIVE GASTROESOPHAGEAL REFLUX DISEASE (GERD)

ACIPHEX® is indicated for short-term (4 to 8 weeks) treatment of 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 EROSION 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

Systemic 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 gastric biopsies. Patients without baseline (105 of 375) patients) had mild or moderate inflammation in the gastric mucosa. Patients with H. pylori infection at the time of inclusion of inflammation in the gastric body tended to moderate, whereas those graded moderate to severe did not. At baseline, 0.5% of patients had atrophy of glands in the gastric body and 15% had atrophy in the gastric antrum. At end point, 0.5% of patients had atrophy point during follow-up, but no consistent changes were seen.

Information for Patients

Patients should be cautioned that ACF/Hx 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 (CYP2C5) drug metabolizing enzyme system. Studies in healthy subjects have shown that rabeprazole does not inhibit, induce, or significantly affect the metabolism of other drugs metabolized by the CYP450 system, such as warfarin and pioglitazone or oral doses. In vitro incubations using human liver microsomes indicated that rabeprazole inhibited cytochrome metabolism with 20 mg of rabeprazole. This degree of inhibition is similar to that by omeprazole or equivalent concentrations.

Rabeprazole produces sustained inhibition of gastric acid secretion. An interaction with the magnitude of acid suppression observed with rabeprazole may occur due to the magnitude of acid suppression observed with high-dose proton pump inhibitors and possibly increase in the AUC of warfarin and co-amoxiclav.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 146-week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumor occurrence in the highest tested dose, and the recommended dose for GERD (20 mg/day) in a 146-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, 50, and 60 mg/kg/day. Rabeprazole produced gastric tumors in male rats. The tumors are of gastric glandular origin. In female rats at all doses included the lowest test human exposure at the recommended dose for GERD. In male rats, no treatment-related tumors were observed in rats at doses up to 60 mg/kg/day. Rabeprazole was positive in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward gene mutation test, and the mouse lymphoma test. Rabeprazole also showed weak inhibition of the human liver cytochrome P450 1A2, 1A2, 1A4, 1B5, 2A6, 2B6, and 3A4. Rabeprazole is a weak inhibitor of human liver cytochrome P450 3A4, and the in vivo rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole is an inhibitor of CYP2C19 isozyme, and the recommended dose for GERD at 60 mg/kg/day (plasma AUC of 8.8-ug/mL, about 10 times the human exposure at the recommended dose for GERD) was found to have effect on the erythrocyte of the human test.
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 qid 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.

HOW SUPPLIED
ACIPHEX® 20 mg is supplied as delayed-release light yellow enteric-coated tablets. The medication code number (E243) is imprinted on one side.

Bottles of 30 (NDC#62856-243-30)
Bottles of 90 (NDC#62856-243-90)
Unit Dose Blister Package of 100 (10 x 10) (NDC#62856-243-41)

Store at 20°C (77°F), excursions permitted to 15-30°C (59-86°F). Protect from moisture.

ACIPHEX® is a registered trademark of Eisai Co., Ltd., Tokyo, Japan.
Manufactured by Eisai Co., Ltd.
Minato, Japan
Made in Japan

Marketed by Eisai Inc., Teaneck, NJ 07666 and Janssen Pharmaceuticals Inc., Titusville, NJ 08560-0200
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