DESCRIPTION

The active ingredient in pantoprazole sodium delayed-release tablets is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1 \(H\)-benzimidazole sesquihydrate, a compound that inhibits gastric acid secretion. The structural formula is:

![Structural formula of pantoprazole sodium sesquihydrate]

\[\text{C}_{16}\text{H}_{14}\text{F}_{2}\text{N}_{3}\text{NaO}_{4}\text{S}\cdot 1.5 \text{H}_{2}\text{O} \text{ M.W. 432.4} \]

Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder and is racemic. Pantoprazole has weakly basic and acidic properties. Pantoprazole sodium sesquihydrate is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane.

The stability of the compound in aqueous solution is pH-dependent. The rate of degradation increases with decreasing pH. At ambient temperature, the degradation half-life is approximately 2.8 hours at pH 5.0 and approximately 220 hours at pH 7.8.

Pantoprazole sodium is supplied as a delayed-release tablet for oral administration, available in 2 strengths. Each delayed-release tablet contains 45.1 mg or 22.6 mg of pantoprazole sodium sesquihydrate (equivalent to 40 mg or 20 mg pantoprazole, respectively) with the following inactive ingredients: antifoam DC 1510, n-butyl alcohol, calcium carbonate, calcium stearate, D&C Yellow #10 Aluminum Lake, FD&C Yellow #6 Aluminum Lake, hypromellose, industrial methylated spirit 74 OP BP, iron oxide black, iron oxide yellow, lactose monohydrate, lecithin, low-substituted hydroxypropyl cellulose, methacrylic acid copolymer, microcrystalline cellulose, polyethylene glycol, propylene glycol, shellac glaze, sodium carbonate anhydrous, stearic acid, talc, titanium dioxide, and triethyl citrate.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Pantoprazole sodium delayed-release tablets are prepared as an enteric-coated tablet so that absorption of pantoprazole begins only after the tablet leaves the stomach. Peak serum concentration (\(C_{\text{max}}\)) and area under the serum concentration time curve (AUC) increase in a manner proportional to oral and intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily dosing. Following oral or intravenous administration, the serum concentration of pantoprazole declines biexponentially with a terminal elimination half-life of approximately one hour. In extensive metabolizers (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Metabolism) with normal liver function receiving an oral dose of the enteric-coated 40 mg pantoprazole tablet, the peak concentration (\(C_{\text{max}}\)) is 2.5 mcg/mL, the time to reach the peak concentration (\(t_{\text{max}}\)) is 2.5 h and the total area under the plasma concentration versus time curve (AUC) is 4.8 mcg•hr/mL. When pantoprazole is given with food, its \(t_{\text{max}}\) is highly variable and may increase significantly. Following intravenous administration of pantoprazole to extensive metabolizers, its total clearance is 7.6 to 14.0 L/h and its apparent volume of distribution is 11.0 to 23.6 L.

Absorption

The absorption of pantoprazole is rapid, with a \(C_{\text{max}}\) of 2.5 mcg/mL that occurs approximately 2.5 hours after single or multiple oral 40 mg doses. Pantoprazole is well absorbed; it undergoes little first-pass metabolism resulting in an absolute bioavailability of approximately 77%. Pantoprazole absorption is not affected by concomitant administration of antacids. Administration of pantoprazole with food may delay its absorption up to 2 hours or longer; however, the \(C_{\text{max}}\) and the extent of pantoprazole absorption (AUC) are not altered. Thus, pantoprazole may be taken without regard to timing of meals.

Distribution

The apparent volume of distribution of pantoprazole is approximately 11.0 to 23.6 L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.
Metabolism
Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g., 3% of Caucasians and African-Americans and 17% to 23% of Asians). Although these sub-populations of slow pantoprazole metabolizers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation (≤ 23%) with once daily dosing.

Elimination
After a single oral or intravenous dose of 14C-labeled pantoprazole to healthy, normal metabolizer volunteers, approximately 71% of the dose was excreted in the urine with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged pantoprazole.

Special Populations

Geriatric
Only slight to moderate increases in pantoprazole AUC (43%) and C max (26%) were found in elderly volunteers (64 to 76 years of age) after repeated oral administration, compared with younger subjects. No dosage adjustment is recommended based on age.

Pediatric
The pharmacokinetics of pantoprazole have not been investigated in patients < 18 years of age.

Gender
There is a modest increase in pantoprazole AUC and C max in women compared to men. However, weight-normalized clearance values are similar in women and men. No dosage adjustment is needed based on gender (see PRECAUTIONS, Use in Women).

Renal impairment
In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole were similar to those of healthy subjects. No dosage adjustment is necessary in patients with renal impairment or in patients undergoing hemodialysis.

Hepatic impairment
In patients with mild to severe hepatic impairment, maximum pantoprazole concentrations increased only slightly (1.5 fold) relative to healthy subjects. Although serum half-life values increased to 7 to 9 hours and AUC values increased by 5 to 7 fold in hepatic-impaired patients, these increases were no greater than those observed in slow CYP2C19 metabolizers, where no dosage frequency adjustment is warranted. These pharmacokinetic changes in hepatic-impaired patients result in minimal drug accumulation following once daily multiple-dose administration. No dosage adjustment is needed in patients with mild to severe hepatic impairment. Doses higher than 40 mg/day have not been studied in hepatically-impaired patients.

Drug-Drug Interactions
Pantoprazole is metabolized mainly by CYP2C19 and to minor extents by CYPs 3A4, 2D6 and 2C9. In in vivo drug-drug interaction studies with CYP2C19 substrates (diazepam [also a CYP3A4 substrate] and phenytoin [also a CYP3A4 inducer]), nifedipine, midazolam, and clarithromycin (CYP3A4 substrates), metoprolol (a CYP2D6 substrate), diclofenac, naproxen and piroxicam (CYP2C9 substrates) and theophylline (a CYP1A2 substrate) in healthy subjects, the pharmacokinetics of pantoprazole were not significantly altered. It is, therefore, expected that other drugs metabolized by CYPs 2C19, 3A4, 2D6, 2C9, and 1A2 would not significantly affect the pharmacokinetics of pantoprazole. In vivo studies also suggest that pantoprazole does not significantly affect the kinetics of other drugs (cisapride, theophylline, diazepam [and its active metabolite, desmethyldiazepam], phenytoin, warfarin, metoprolol, nifedipine, carbamazepine, midazolam, clarithromycin, naproxen, piroxicam, and oral contraceptives [levonorgestrel/ethyl estradiol]) metabolized by CYPs 2C19, 3A4, 2C9, 2D6, and 1A2. Therefore, it is expected that pantoprazole would not significantly affect the pharmacokinetics of other drugs metabolized by these isozymes. Dosage adjustment of such drugs is not necessary when they are coadministered with pantoprazole. In other in vivo studies, digoxin, ethanol, glyburide, antipyrine, caffeine, metronidazole, and amoxicillin had no clinically relevant interactions with pantoprazole. Although no significant drug-drug interactions have been observed in clinical studies, the potential for significant drug-drug interactions with more than once daily dosing with high doses of pantoprazole has not been studied in poor metabolizers or individuals who are hepatically impaired.

Pharmacodynamics

Mechanism of Action
Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by covalently binding to the (H+K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and
stimulated gastric acid secretion irrespective of the stimulus. The binding to the \((H^+,K^+)-ATPase\) results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested.

Antisecretory Activity

Under maximal acid stimulatory conditions using pentagastrin, a dose-dependent decrease in gastric acid output occurs after a single dose of oral (20 to 80 mg) or a single dose of intravenous (20 to 120 mg) pantoprazole in healthy volunteers. Pantoprazole given once daily results in increasing inhibition of gastric acid secretion. Following the initial oral dose of 40 mg pantoprazole, a 51% mean inhibition was achieved by 2.5 hours. With once a day dosing for 7 days the mean inhibition was increased to 85%. Pantoprazole suppressed acid secretion in excess of 95% in half of the subjects. Acid secretion had returned to normal within a week after the last dose of pantoprazole; there was no evidence of rebound hypersecretion.

In a series of dose-response studies pantoprazole, at oral doses ranging from 20 to 120 mg, caused dose-related increases in median basal gastric \(pH\) and in the percent of time gastric \(pH\) was > 3 and > 4. Treatment with 40 mg of pantoprazole produced optimal increases in gastric \(pH\) which were significantly greater than the 20 mg dose. Doses higher than 40 mg (60, 80, 120 mg) did not result in further significant increases in median gastric \(pH\). The effects of pantoprazole on median \(pH\) from one double-blind crossover study are shown below.

**Effect of Single Daily Doses of Oral Pantoprazole on Intragastric \(pH\)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 a.m. to 8 a.m. (24 hours)</td>
<td>1.3</td>
<td>2.9*</td>
<td>3.8*#</td>
<td>3.9*#</td>
</tr>
<tr>
<td>8 a.m. to 10 p.m. (Daytime)</td>
<td>1.6</td>
<td>3.2*</td>
<td>4.4*#</td>
<td>4.8*#</td>
</tr>
<tr>
<td>10 p.m. to 8 a.m. (Nighttime)</td>
<td>1.2</td>
<td>2.1*</td>
<td>3.0*</td>
<td>2.6*</td>
</tr>
</tbody>
</table>

*Significantly different from placebo
#Significantly different from 20 mg

Serum Gastrin Effects

Fasting serum gastrin levels were assessed in two double-blind studies of the acute healing of erosive esophagitis (EE) in which 682 patients with gastroesophageal reflux disease (GERD) received 10, 20, or 40 mg of pantoprazole for up to 8 weeks. At 4 weeks of treatment there was an increase in mean gastrin levels of 7%, 35%, and 72% over pretreatment values in the 10, 20, and 40 mg treatment groups, respectively. A similar increase in serum gastrin levels was noted at the 8 week visit with mean increases of 3%, 26%, and 84% for the three pantoprazole dose groups. Median serum gastrin levels remained within normal limits during maintenance therapy with pantoprazole delayed-release tablets.

In long-term international studies involving over 800 patients, a 2 to 3 fold mean increase from the pretreatment fasting serum gastrin level was observed in the initial months of treatment with pantoprazole at doses of 40 mg per day during GERD maintenance studies and 40 mg or higher per day in patients with refractory GERD. Fasting serum gastrin levels generally remained at approximately 2 to 3 times baseline for up to 4 years of periodic follow-up in clinical trials.

Following healing of gastric or duodenal ulcers with pantoprazole treatment, elevated gastrin levels return to normal by at least 3 months.

Enterochromaffin-Like (ECL) Cell Effects

In 39 patients treated with oral pantoprazole 40 mg to 240 mg daily (majority receiving 40 mg to 80 mg) for up to 5 years, there was a moderate increase in ECL-cell density starting after the first year of use which appeared to plateau after 4 years.

In a nonclinical study in Sprague-Dawley rats, lifetime exposure (24 months) to pantoprazole at doses of 0.5 to 200 mg/kg/day resulted in dose-related increases in gastric ECL-cell proliferation and gastric neuroendocrine (NE)-cell tumors. Gastric NE-cell tumors in rats may result from chronic elevation of serum gastrin concentrations. The high density of ECL cells in the rat stomach makes this species highly susceptible to the proliferative effects of elevated gastrin concentrations produced by proton pump inhibitors. However, there were no observed elevations in serum gastrin following the administration of pantoprazole at a dose of 0.5 mg/kg/day. In a separate study, a gastric NE-cell tumor without concomitant ECL-cell proliferative changes was observed in 1 female rat following 12 months of dosing with pantoprazole at 5 mg/kg/day and a 9 month off-dose recovery (see **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility**).
Other Effects
No clinically relevant effects of pantoprazole on cardiovascular, respiratory, ophthalmic, or central nervous system function have been detected. In a clinical pharmacology study, pantoprazole 40 mg given once daily for 2 weeks had no effect on the levels of the following hormones: cortisol, testosterone, triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), thyronine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, and growth hormone.

In a 1 year study of GERD patients treated with pantoprazole 40 mg or 20 mg, there were no changes from baseline in overall levels of T3, T4, and TSH.

Clinical Studies
Pantoprazole delayed-release tablets were used in all clinical trials.

Erosive Esophagitis (EE) Associated With Gastroesophageal Reflux Disease (GERD)
A U.S. multicenter double-blind, placebo-controlled study of pantoprazole 10 mg, 20 mg, or 40 mg once daily was conducted in 603 patients with reflux symptoms and endoscopically diagnosed EE of grade 2 or above (Hetzel-Dent scale). In this study, approximately 25% of enrolled patients had severe EE of grade 3 and 10% had grade 4. The percentages of patients healed (per protocol, n = 541) in this study were as follows:

<table>
<thead>
<tr>
<th>Erosive Esophagitis Healing Rates (per Protocol)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pantoprazole</strong></td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Week</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>8</td>
</tr>
</tbody>
</table>

*(p < 0.001) pantoprazole versus placebo.
*(p < 0.05) versus 10 mg or 20 mg pantoprazole
#(p < 0.05) versus 10 mg pantoprazole

In this study, all pantoprazole treatment groups had significantly greater healing rates than the placebo group. This was true regardless of *H. pylori* status for the 40 mg and 20 mg pantoprazole treatment groups. The 40 mg dose of pantoprazole resulted in healing rates significantly greater than those found with either the 20 or 10 mg dose.

A significantly greater proportion of patients taking pantoprazole 40 mg experienced complete relief of daytime and nighttime heartburn and the absence of regurgitation starting from the first day of treatment compared with placebo. Patients taking pantoprazole consumed significantly fewer antacid tablets per day than those taking placebo.

Pantoprazole 40 mg and 20 mg once daily were also compared with nizatidine 150 mg twice daily in a U.S. multicenter, double-blind study of 243 patients with reflux symptoms and endoscopically diagnosed EE of grade 2 or above. The percentages of patients healed (per protocol, n = 212) were as follows:

<table>
<thead>
<tr>
<th>Erosive Esophagitis Healing Rates (per Protocol)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pantoprazole</strong></td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Week</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>8</td>
</tr>
</tbody>
</table>

*(p < 0.001) pantoprazole versus nizatidine.

Once daily treatment with pantoprazole 40 mg or 20 mg resulted in significantly superior rates of healing at both 4 and 8 weeks compared with twice daily treatment with 150 mg of nizatidine. For the 40 mg treatment group, significantly greater healing rates compared to nizatidine were achieved regardless of the *H. pylori* status.
A significantly greater proportion of the patients in the pantoprazole treatment groups experienced complete relief of nighttime heartburn and regurgitation starting on the first day and of daytime heartburn on the second day compared with those taking nizatidine 150 mg twice daily. Patients taking pantoprazole consumed significantly fewer antacid tablets per day than those taking nizatidine.

Long-Term Maintenance of Healing of Erosive Esophagitis
Two independent, multicenter, randomized, double-blind, comparator-controlled trials of identical design were conducted in GERD patients with endoscopically-confirmed healed erosive esophagitis to demonstrate efficacy of pantoprazole in long-term maintenance of healing. The two U.S. studies enrolled 386 and 404 patients, respectively, to receive either 10 mg, 20 mg, or 40 mg of pantoprazole delayed-release tablets once daily or 150 mg of ranitidine twice daily. As demonstrated in the table below, pantoprazole 40 mg and 20 mg were significantly superior to ranitidine at every time point with respect to the maintenance of healing. In addition, pantoprazole 40 mg was superior to all other treatments studied.

Long-Term Maintenance of Healing of Erosive Gastroesophageal Reflux Disease (GERD Maintenance): Percentage of Patients Who Remained Healed

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Pantoprazole 20 mg QD</th>
<th>Pantoprazole 40 mg QD</th>
<th>Ranitidine 150 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 75</td>
<td>n = 74</td>
<td>n = 75</td>
</tr>
<tr>
<td>Month 1</td>
<td>91*</td>
<td>99*</td>
<td>68</td>
</tr>
<tr>
<td>Month 3</td>
<td>82*</td>
<td>93*#</td>
<td>54</td>
</tr>
<tr>
<td>Month 6</td>
<td>76*</td>
<td>90*#</td>
<td>44</td>
</tr>
<tr>
<td>Month 12</td>
<td>70*</td>
<td>86*#</td>
<td>35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study 2</th>
<th>n = 74</th>
<th>n = 88</th>
<th>n = 84</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>89*</td>
<td>92*#</td>
<td>62</td>
</tr>
<tr>
<td>Month 3</td>
<td>78*</td>
<td>91*#</td>
<td>47</td>
</tr>
<tr>
<td>Month 6</td>
<td>72*</td>
<td>88*#</td>
<td>39</td>
</tr>
<tr>
<td>Month 12</td>
<td>72*</td>
<td>83*</td>
<td>37</td>
</tr>
</tbody>
</table>

* (p < 0.05 vs ranitidine)
# (p < 0.05 vs pantoprazole 20 mg)

Note: Pantoprazole 10 mg was superior (p < 0.05) to ranitidine in study 2 but not study 1.

Pantoprazole 40 mg was superior to ranitidine in reducing the number of daytime and nighttime heartburn episodes from the first through the twelfth month of treatment. Pantoprazole 20 mg, administered once daily, was also effective in reducing episodes of daytime and nighttime heartburn in one trial.

Number of Episodes of Heartburn (Mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Pantoprazole 40 mg QD</th>
<th>Ranitidine 150 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime</td>
<td>5.1 ± 1.6*</td>
<td>18.3 ± 1.6</td>
</tr>
<tr>
<td>Nighttime</td>
<td>3.9 ± 1.1*</td>
<td>11.9 ± 1.1</td>
</tr>
<tr>
<td>Month 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime</td>
<td>2.9 ± 1.5*</td>
<td>17.5 ± 1.5</td>
</tr>
<tr>
<td>Nighttime</td>
<td>2.5 ± 1.2*</td>
<td>13.8 ± 1.3</td>
</tr>
</tbody>
</table>

* (p < 0.001 vs ranitidine, combined data from the 2 U.S. studies)

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
In a multicenter, open-label trial of 35 patients with pathological hypersecretory conditions, such as Zollinger-Ellison syndrome with or without multiple endocrine neoplasia-type I, pantoprazole successfully controlled gastric acid secretion. Doses ranging from 80 mg daily to 240 mg daily maintained gastric acid output below 10 mEq/h in patients without prior acid-reducing surgery and below 5 mEq/h in patients with prior acid-reducing surgery.
Doses were initially titrated to the individual patient needs, and adjusted in some patients based on the clinical response with time (see DOSAGE AND ADMINISTRATION). Pantoprazole was well tolerated at these dose levels for prolonged periods (greater than 2 years in some patients).

INDICATIONS AND USAGE

Short-Term Treatment of Erosive Esophagitis Associated With Gastroesophageal Reflux Disease (GERD)
Pantoprazole sodium delayed-release tablets are indicated for the short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis. For those patients who have not healed after 8 weeks of treatment, an additional 8 week course of pantoprazole sodium delayed-release tablets may be considered.

Maintenance of Healing of Erosive Esophagitis
Pantoprazole sodium delayed-release tablets are indicated for maintenance of healing of erosive esophagitis and reduction in relapse rates of daytime and nighttime heartburn symptoms in patients with gastroesophageal reflux disease (GERD). Controlled studies did not extend beyond 12 months.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
Pantoprazole sodium delayed-release tablets are indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

CONTRAINDICATIONS
Pantoprazole sodium delayed-release tablets are contraindicated in patients with known hypersensitivity to any component of the formulation.

PRECAUTIONS

General
Symptomatic response to therapy with pantoprazole does not preclude the presence of gastric malignancy. Owing to the chronic nature of erosive esophagitis, there may be a potential for prolonged administration of pantoprazole. In long-term rodent studies, pantoprazole was carcinogenic and caused rare types of gastrointestinal tumors. The relevance of these findings to tumor development in humans is unknown. Generally, daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (Vitamin B-12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This possibility should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.
Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with pantoprazole, particularly in patients who were H. pylori positive.

Information for Patients
Patients should be cautioned that pantoprazole sodium delayed-release tablets should not be split, crushed or chewed. The tablets should be swallowed whole, with or without food in the stomach. Concomitant administration of antacids does not affect the absorption of pantoprazole.

Drug Interactions
Pantoprazole is metabolized through the cytochrome P450 system, primarily the CYP2C19 and CYP3A4 isozymes, and subsequently undergoes Phase II conjugation (see CLINICAL PHARMACOLOGY, Drug-Drug Interactions). Based on studies evaluating possible interactions of pantoprazole with other drugs, no dosage adjustment is needed with concomitant use of the following: theophylline, cisapride, antipyrene, caffeine, carbamazepine, diazepam (and its active metabolite, desmethyldiazepam), diclofenac, naproxen, piroxicam, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinyl estradiol), metoprolol, nifedipine, phenytoin, warfarin (see below), midazolam, clarithromycin, metronidazole, or amoxicillin. Clinically relevant interactions of pantoprazole with other drugs with the same metabolic pathways are not expected. Therefore, when coadministered with pantoprazole, adjustment of the dosage of pantoprazole or of such drugs may not be necessary. There was also no interaction with concomitantly administered antacids. There have been postmarketing reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including pantoprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly should be monitored for increases in INR and prothrombin time.
Concomitant use of atazanavir and proton pump inhibitors is not recommended. Coadministration of atazanavir with proton pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and thereby reduce its therapeutic effect. Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).
Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24 month carcinogenicity study, Sprague-Dawley rats were treated orally with doses of 0.5 to 200 mg/kg/day, about 0.1 to 40 times the exposure on a body surface area basis of a 50 kg person dosed at 40 mg/day. In the gastric fundus, treatment at 0.5 to 200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment at 50 and 200 mg/kg/day (about 10 and 40 times the recommended human dose on a body surface area basis) produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum at 50 mg/kg/day, and benign polyps and adenocarcinomas of the gastric fundus at 200 mg/kg/day. In the liver, treatment at 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment at 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.

Erosive esophagitis healing rates in the 107 elderly patients (≥ 65 years old) treated with pantoprazole were similar to those found in patients under the age of 65. The incidence rates of adverse events and laboratory abnormalities in patients aged 65 years and older were similar to those associated with patients younger than 65 years of age.
Laboratory Tests
There have been reports of false-positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving most proton pump inhibitors, including pantoprazole. An alternative confirmatory method should be considered to verify positive results.

ADVERSE REACTIONS
Worldwide, more than 11,100 patients have been treated with pantoprazole in clinical trials involving various dosages and duration of treatment. In general, pantoprazole has been well tolerated in both short-term and long-term trials.

In two U.S. controlled clinical trials involving pantoprazole 10, 20, or 40 mg doses for up to 8 weeks, there were no dose-related effects on the incidence of adverse events. The following adverse events considered by investigators to be possibly, probably or definitely related to drug occurred in 1% or more in the individual studies of GERD patients on therapy with pantoprazole.

Most Frequent Adverse Events Reported as Drug Related in Short-Term Domestic Trials

<table>
<thead>
<tr>
<th>Study Event</th>
<th>Pantoprazole (n = 521)</th>
<th>Placebo (n = 82)</th>
<th>Pantoprazole (n = 161)</th>
<th>Nizatidine (n = 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>6</td>
<td>6</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>1</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Rash</td>
<td>&lt; 1</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Eructation</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>&lt; 1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1</td>
<td>0</td>
<td>&lt; 1</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: Only adverse events with an incidence greater than or equal to the comparators are shown.

In international short-term, double-blind or open-label, clinical trials involving 20 to 80 mg per day, the following adverse events were reported to occur in 1% or more of 2805 GERD patients receiving pantoprazole for up to 8 weeks.

Adverse Events in GERD Patients in Short-Term International Trials

<table>
<thead>
<tr>
<th>Study Event</th>
<th>Pantoprazole Total (N = 2805)</th>
<th>Ranitidine 300 mg (N = 594)</th>
<th>Omeprazole 20 mg (N = 474)</th>
<th>Famotidine 40 mg (N = 239)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>1</td>
<td>1</td>
<td>&lt; 1</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

In two U.S. controlled clinical trials involving pantoprazole 10, 20, or 40 mg doses for up to 12 months, the following adverse events considered by investigators to be possibly, probably, or definitely related to drug occurred in 1% or more of GERD patients on long-term therapy.

Most Frequent Adverse Events Reported as Drug Related in Long-Term Domestic Trials

<table>
<thead>
<tr>
<th>Study Event</th>
<th>Pantoprazole (n = 536)</th>
<th>Ranitidine (n = 185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Liver function tests abnormal</td>
<td>2</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Note: Only adverse events with an incidence greater than or equal to the comparators are shown.

In addition, in these short- and long-term domestic and international trials, the following treatment-emergent events, regardless of causality, occurred at a rate of ≥ 1% in pantoprazole-treated patients: anxiety, arthralgia, asthenia, back pain, bronchitis, chest pain, constipation, cough increased, dizziness, dyspepsia, dyspnea, flu syndrome, gastroenteritis, gastrointestinal disorder, hyperlipemia, hypertonia, infection, liver function tests abnormal, migraine, nausea, neck pain, pain, pharyngitis, rectal disorder, rhinitis, SGPT increased, sinusitis, upper respiratory tract infection, urinary frequency, urinary tract infection, and vomiting.

Additional treatment-emergent adverse experiences occurring in < 1% of pantoprazole-treated patients from these trials are listed below by body system. In most instances the relationship to pantoprazole was unclear.
BODY AS A WHOLE: abscess, allergic reaction, chills, cyst, face edema, fever, generalized edema, heat stroke, hernia, laboratory
test abnormal, malaise, moniliasis, neoplasm, non-specified drug reaction, photosensitivity reaction.
CARDIOVASCULAR SYSTEM: abnormal electrocardiogram, angina pectoris, arrhythmia, atrial fibrillation/flutter, cardiovascular
disorder, chest pain substernal, congestive heart failure, hemorrhage, hypertension, hypotension, myocardial infarction, myocardial
ischemia, palpitation, retinal vascular disorder, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation.
DIGESTIVE SYSTEM: anorexia, aphthous stomatitis, cardiopasm, colitis, dry mouth, duodenitis, dysphagia, enteritis, esophageal
hemorrhage, esophagitis, gastrointestinal carcinoma, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, glossitis,
halitosis, hematemesis, increased appetite, melena, mouth ulceration, oral moniliasis, periodontal abscess, periodontitis, rectal
hemorrhage, stomach ulcer, stomatitis, stools abnormal, tongue discoloration, ulcerative colitis.
ENDOCRINE SYSTEM: diabetes mellitus, glycosuria, goiter.
HEPATO-BILIARY SYSTEM: biliary pain, hyperbilirubinemia, cholecystitis, cholelithiasis, choledastic jaundice, hepatitis, alkaline
phosphatase increased, gamma glutamyl transpeptidase increased, SGOT increased.
HEMIC AND LYMPHATIC SYSTEM: anemia, ecchymosis, eosinophilia, hypochromic anemia, iron deficiency anemia,
leukocytosis, leukopenia, thrombocytopenia.
METABOLIC AND NUTRITIONAL: dehydration, edema, gout, peripheral edema, thirst, weight gain, weight loss.
MUSCULOSKELETAL SYSTEM: arthritis, arthrosis, bone disorder, bone pain, bursitis, joint disorder, leg cramps, neck rigidity,
myalgia, tenosynovitis.
NERVOUS SYSTEM: abnormal dreams, confusion, convulsion, depression, dry mouth, dysarthria, emotional lability, hallucinations,
hyperkinesia, hypesthesia, libido decreased, nervousness, neuralgia, neuritis, neuropathy, paresthesia, reflexes decreased, sleep
disorder, somnolence, thinking abnormal, tremor, vertigo.
RESPIRATORY SYSTEM: asthma, epistaxis, hiccup, laryngitis, lung disorder, pneumonia, voice alteration.
SKIN AND APPENDAGES: acne, alopecia, contact dermatitis, dry skin, eczema, fungal dermatitis, hemorrhage, herpes simplex,
herpes zoster, lichenoid dermatitis, maculopapular rash, pruritus, skin disorder, skin ulcer, sweating, urticaria.
SPECIAL SENSES: abnormal vision, amblyopia, cataaract specified, deafness, diplopia, ear pain, extraocular palsy, glaucoma, oitis externa,
taste perversion, tinnitus.
UROGENITAL SYSTEM: albuminuria, balanitis, breast pain, cystitis, dysmenorrhea, dysuria, epididymitis, hematuria, impotence,
kidney calculus, kidney pain, nocturia, prostatic disorder, pyelonephritis, scrotal edema, urethral pain, urethritis, urinary tract disorder,
urination impaired, vaginitis.

In an open-label U.S. clinical trial conducted in 35 patients with pathological hypersecretory conditions treated with pantoprazole for
up to 27 months, the adverse events reported were consistent with the safety profile of the drug in other populations.

Postmarketing Reports
There have been spontaneous reports of adverse events with the postmarketing use of pantoprazole. These reports include the
following:
BODY AS A WHOLE: anaphylaxis (including anaphylactic shock), angioedema (Quincke’s edema).
DIGESTIVE SYSTEM: increased salivation, nausea, pancreatitis.
HEMATIC AND LYMPHATIC SYSTEM: pancytopenia.
HEPATO-BILIARY SYSTEM: hepatocellular damage leading to jaundice and hepatic failure.
MUSCULOSKELETAL SYSTEM: elevated CPK (creatinine phosphokinase), rhabdomyolysis.
NERVOUS SYSTEM: confusion, hypokinesia, speech disorder, vertigo.
SKIN AND APPENDAGES: severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic
epidermal necrolysis (TEN, some fatal).
SPECIAL SENSES: anterior ischemic optic neuropathy, blurred vision, tinnitus.
UROGENITAL SYSTEM: interstitial nephritis.

Laboratory Values
In two U.S. controlled, short-term trials in patients with erosive esophagitis associated with GERD, 0.4% of the patients on
pantoprazole 40 mg experienced SGPT elevations of greater than three times the upper limit of normal at the final treatment visit.
In two U.S. controlled, long-term trials in patients with erosive esophagitis associated with GERD, none of 178 patients (0%) on
pantoprazole 40 mg and two of 181 patients (1.1%) on pantoprazole 20 mg experienced significant transaminase elevations at 12
months (or earlier if a patient discontinued prematurely). Significant elevations of SGOT or SGPT were defined as values at least
three times the upper limit of normal that were non-sporadic and had no clear alternative explanation. The following changes in
laboratory parameters were reported as adverse events; creatinine increased, hypercholesterolemia, and hyperuricemia.

OVERDOSE
Experience in patients taking very high doses of pantoprazole is limited. There have been spontaneous reports of overdosage with
pantoprazole, including a suicide in which pantoprazole 560 mg and undetermined amounts of chloroquine and zopiclone were also
ingested. There have also been spontaneous reports of patients taking similar amounts of pantoprazole (400 mg and 600 mg) with no
adverse effects.
Pantoprazole is not removed by hemodialysis. In case of overdosage, treatment should be symptomatic and supportive.
Single oral doses of pantoprazole at 709 mg/kg, 798 mg/kg, and 887 mg/kg were lethal to mice, rats, and dogs, respectively. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

DOSAGE AND ADMINISTRATION

Treatment of Erosive Esophagitis
The recommended adult oral dose is 40 mg given once daily for up to 8 weeks. For those patients who have not healed after 8 weeks of treatment, an additional 8 week course of pantoprazole may be considered (see INDICATIONS AND USAGE).

Maintenance of Healing of Erosive Esophagitis
The recommended adult oral dose is one pantoprazole sodium delayed-release tablet 40 mg, taken daily (see CLINICAL PHARMACOLOGY, Clinical Studies).

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
The dosage of pantoprazole in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult starting dose is 40 mg twice daily. Dosage regimens should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 240 mg daily have been administered. Some patients have been treated continuously with pantoprazole for more than 2 years.

No dosage adjustment is necessary in patients with renal impairment, hepatic impairment, or for elderly patients. Doses higher than 40 mg/day have not been studied in hepatically-impaired patients. No dosage adjustment is necessary in patients undergoing hemodialysis.

Pantoprazole sodium delayed-release tablets should be swallowed whole, with or without food in the stomach. If patients are unable to swallow a 40 mg tablet, two 20 mg tablets may be taken. Concomitant administration of antacids does not affect the absorption of pantoprazole.

Patients should be cautioned that pantoprazole sodium delayed-release tablets should not be split, chewed or crushed.

HOW SUPPLIED
Pantoprazole sodium delayed-release tablets are available as:
20 mg - yellow, oval shaped tablets imprinted with black ink on one side of the tablet “93/11” and blank on the other side. They are available in:

<table>
<thead>
<tr>
<th>NDC 54868-6038-0</th>
<th>Bottles of 30</th>
</tr>
</thead>
</table>

40 mg - yellow, oval shaped tablets imprinted with black ink on one side of the tablet “93/12” and blank on the other side. They are available in:

<table>
<thead>
<tr>
<th>NDC 54868-5846-3</th>
<th>Bottles of 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDC 54868-5846-0</td>
<td>Bottles of 30</td>
</tr>
<tr>
<td>NDC 54868-5846-2</td>
<td>Bottles of 60</td>
</tr>
<tr>
<td>NDC 54868-5846-1</td>
<td>Bottles of 90</td>
</tr>
</tbody>
</table>

Storage
Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Manufactured In Israel By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Relabeling and Repackaging by:
Physicians Total Care, Inc.
Tulsa, Oklahoma  74146
PANTOPRAZOLE SODIUM Delayed-Release Tablets 20 mg* Rx only

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