PREVACID®FDT
(Lansoprazole Fast Disintegrating Tablets)

1. PRODUCT NAME
PREVACID® FDT 15
PREVACID® FDT 30

2. NAME AND STRENGTH OF ACTIVE INGREDIENT
PREVACID® FDT 15: Each tablet contains Lansoprazole 15 mg
PREVACID® FDT 30: Each tablet contains Lansoprazole 30 mg

3. PRODUCT DESCRIPTION
PREVACID®FDT are white to yellowish white uncoated tablets with orange to dark brown speckles for oral administration containing the active ingredient, lansoprazole in the form of enteric-coated microgranules.

4. PHARMACODYNAMIC/PHARMACOKINETICS
PREVACID® FDT is a preparation of lansoprazole, a proton pump inhibitor.
PREVACID® FDT inhibits the gastric acid secretion strongly and sustainedly by suppressing the activity of (H^+-K^+)-ATPase which is locally existed in the parietal cells of gastric mucosa and plays an important role as a proton pump.

Clinically, PREVACID® FDT attains a rapid and high healing ratio against gastric ulcer and duodenal ulcer, and the usefulness of the drug has been proved. It has also been proved to be a useful drug for treatment of stomal ulcer, reflux esophagitis and Zollinger-Ellison syndrome.

Pharmacodynamics
Mechanism of Action
Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of the (H^+,K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. Lansoprazole does not exhibit anticholinergic or histamine type-2 antagonist activity.

Pharmacokinetics
PREVACID® FDT contains an enteric-coated granule formulation of lansoprazole. Absorption of lansoprazole begins only after the granules leave the stomach. Absorption is rapid, with mean peak plasma levels of lansoprazole occurring after approximately 1.7 hours. Peak plasma concentrations of lansoprazole (C_{max}) and the area under the plasma concentration curve (AUC) of lansoprazole are approximately proportional in doses from 15 mg to 60 mg after single-oral administration. Lansoprazole does not accumulate and its pharmacokinetics are unaltered by multiple dosing.

Absorption

The absorption of lansoprazole is rapid, with mean C_{max} occurring approximately 1.7 hours after oral dosing, and relatively complete with absolute bioavailability over 80%. In healthy subjects, the mean (±SD) plasma half-life was 1.5 (±1.0) hours. Both C_{max} and AUC are diminished by about 50% to 70 % if the drug is given 30 minutes after food as opposed to the fasting condition. There is no significant food effect if the drug is given before meals.

Distribution

Lansoprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0.05 to 5.0 µg/mL.

Metabolism

Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory activity. Lansoprazole is thought to be transformed into two active species which inhibit acid secretion by (H^+,K^+)-ATPase within the parietal cell canaliculus, but are not present in the systemic circulation. The plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion. Thus, the plasma elimination half-life is less than two hours, while the acid inhibitory effect lasts more than 24 hours.

Elimination

Following single-dose oral administration of lansoprazole, virtually no unchanged lansoprazole was excreted in the urine. In one study, after a single oral dose of ^{14}C-lansoprazole, approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the feces. This implies a significant biliary excretion of the metabolites of lansoprazole.

Special Populations

Geriatric

The clearance of lansoprazole is decreased in the elderly, with elimination half-life increased approximately 50% to 100%. Because the mean half-life in the elderly remains between 1.9 to 2.9 hours, repeated once daily dosing does not result in accumulation of lansoprazole. Peak plasma levels were not increased in the elderly.

Pediatric

One to 17 years of age

The pharmacokinetics of lansoprazole were studies in pediatric patients with GERD aged 1 to 11 years and 12 to 17 years in two separate clinical studies. In children aged 1 to 11 years, lansoprazole was dosed 15 mg q.d. for subjects weighing ≤ 30 kg and 30 mg q.d. for subjects weighing > 30 kg. Mean C_{max} and AUC values observed on Day 5 of dosing were similar between the two dose groups and were not affected by weight or age within each weight-adjusted dose group used in the study. In adolescent subjects aged 12 to 17 years, subjects were randomized to receive lansoprazole at 15 mg or 30 mg q.d. Mean C_{max} and AUC values of lansoprazole was not affected by bodyweight or age; and nearly dose-proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall,

lansoprazole pharmacokinetic patients aged 1 to 17 years were similar to those observed in healthy adult subjects.

Gender

In a study comparing 12 male and 6 female human subjects who received lansoprazole, no gender differences were found in pharmacokinetics and intragastric pH results. =

Renal impairment

In patients with severe renal impairment, plasma protein binding decreased by 1.0%-1.5% after administration of 60 mg of lansoprazole. Patients with renal impairment had a shortened elimination half-life and decreased total AUC (free and bound). AUC for free lansoprazole in plasma, however, was not related to the degree of renal impairment, and C_{max} and T_{max} (time to reach the maximum concentration) were not different than the C_{max} and T_{max} from subjects with normal renal function.

Therefore, the pharmacokinetics of lansoprazole were not clinically different in patients with mild, moderate or severe renal impairment compared to healthy subjects with normal renal function.

Hepatic impairment

In patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment there was an approximate 3-fold increase in mean AUC compared to healthy subjects with normal hepatic function following multiple oral doses of 30 mg PREVACID for 7 days. The corresponding mean plasma half-life of lansoprazole was prolonged from 1.5 hours to 4 hours (Child-Pugh A) or 5 hours (Child-Pugh B).

In patients with compensated and decompensated cirrhosis, there was an approximate 6- and 5-fold increase in AUC, respectively, compared to healthy subjects with normal hepatic function following a single oral dose of 30 mg PREVACID [see Recommended Dose, Special Population].

Drug-Drug Interaction

Effect of Lansoprazole on Other Drugs

Cytochrome P450 Interactions:

Lansoprazole is metabolized through the cytochrome P450 system, specifically through the CYP3A and CYP2C19 isozymes. Studies have shown that lansoprazole does not have clinically significant interactions with other drugs metabolized by the cytochrome P450 system such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propanolol, prednisolone, diazepam, clarithromycin, or terfenadine in healthy subjects. These compounds are metabolized through various cytochrome P450 isozymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A.

Theophylline: When lansoprazole was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of theophylline was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction has not been considered to be clinically concern.

Methotrexate and 7-hydromethotrexate: In an open-label, single-arm, eight-day, pharmacokinetic study of 28 adult rheumatoid arthritis patients (who required the chronic use of 7.5 to 15 mg of methotrexate given weekly), administration of 7 days of naproxen 500 mg twice daily and PREVACID® 30 mg daily had no effect on the pharmacokinetics of methotrexate and 7-hydroxymethotrexate. While this study was not designed to assess the safety of this combination of drugs, no major adverse reactions were noted. However, this study was conducted with low doses of methotrexate. A drug interaction study with high doses of methotrexate has not been conducted.

Amoxicillin: Lansoprazole has also been shown to have no clinically significant interaction with amoxicillin.

Sucralfate: In a single-dose crossover study examining lansoprazole 30 mg administered alone and concomitantly with sucralfate 1 gram, absorption of lansoprazole was delayed and their bioavailability was reduced by 17% when administered concomitantly with sucralfate.

Antacids:
In clinical trials, antacids were administered concomitantly with PREVACID and there was no evidence of a change in the efficacy of PREVACID.

Clopidogrel: Clopidogrel is metabolized to its active metabolite in part by CYP2C19. A study of healthy subjects who were CYP2C19 extensive metabolizers, receiving once daily administration of clopidogrel 75 mg alone or concomitantly with PREVACID® 30 mg (n=40), for 9 days was conducted. The mean AUC of the active metabolite of clopidogrel was reduced by approximately 14% (mean AUC ratio was 86%, with 90% CI of 80 to 92%) when PREVACID was co-administered compared to administration of clopidogrel alone.

Pharmacodynamic parameters were also measured and demonstrated that the change in inhibition of platelet aggregation (induced by 5 mcM ADP) was related to the change in the exposure to clopidogrel active metabolite. The effect on exposure to the active metabolite of clopidogrel and on clopidogrel-induced platelet inhibition is not considered clinically important.

Effect of Other Drugs on Lansoprazole
Because lansoprazole is metabolized by CYP2C19 and CYP3A4, inducers and inhibitors of these enzymes may potentially alter exposure of lansoprazole

5. INDICATIONS

- Gastric ulcer, duodenal ulcer, stomal ulcer and reflux esophagitis.
- Relief of reflux-like symptoms (e.g., heartburn) and/or ulcer-like symptoms (e.g., upper epigastric pain) associated with acid-related dyspepsia.
- Treatment and prophylaxis of NSAID-associated benign gastric ulcers, duodenal ulcers and relief of symptoms in patients requiring continued NSAID treatment.
- Eradication of *H. pylori* from the upper gastrointestinal tract in patients with peptic ulcer (duodenal or benign gastric ulcer) when used in combination with appropriate antibiotics.
- Maintenance treatment of healed duodenal ulcer.
- Maintenance treatment of erosive esophagitis.

- Gastroesophageal Reflux Disease (GERD).
- Zollinger-Ellison syndrome (and other pathological hypersecretory condition).
- Short-term treatment of symptomatic GERD and erosive esophagitis for children (1-17 years of age).

6. RECOMMENDED DOSE

Indication	Dose	Frequency
Duodenal Ulcers		
Short-Term Treatment	30 mg	Once daily for 4 weeks
Maintenance of Healed	15 mg	Once daily
***H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence#**		
Triple Therapy:		
PREVACID® FDT	30 mg	Twice daily (q12h) for 7 days
Amoxicillin	1 gram	Twice daily (q12h) for 7 days
(or Metronidazole)	(400 mg)	(Twice daily (q12h) for 7 days)
Clarithromycin	250-500 mg	Twice daily (q12h) for 7 days
Benign Gastric Ulcer and Stomal Ulcer		
Short-Term Treatment	30 mg	Once daily for 8 weeks
Reflux Esophagitis	30 mg	Once daily for 4-8 weeks
Acid-Related Dyspepsia	15 or 30 mg	Once daily for 2-4 weeks*
NSAID-Associated Benign Gastric and Duodenal Ulcer and Relief of Symptom		
Treatment	15 or 30mg	Once daily for 4-8 weeks**
Prophylaxis	15 or 30 mg	Once daily
Gastroesophageal Reflux Disease (GERD)		
Short-Term Treatment of Symptomatic GERD	15 mg	Once daily for up to 8 weeks
Short-Term Treatment of Erosive Esophagitis	30 mg	Once daily for up to 8 weeks+
Maintenance of Healing of Erosive Esophagitis	15 mg	Once daily
Zollinger-Ellison Syndrome (and Other Pathological Hypersecretory Condition)	60 mg	Once daily***
Pediatric		
Pediatric Patients 1 to 11 Years of Age		
In clinical studies, PREVACID was not administered beyond 12 weeks in 1 to 11 year olds. It is not known if PREVACID is safe and effective if used longer than the recommended duration. Do not exceed the recommended dose and duration of use in pediatric patients as outlined below.		
Short-Term Treatment of Symptomatic GERD and, Short-Term Treatment of Erosive Esophagitis		
≤ 30 kg	15 mg	Once daily for up to 12 weeks
> 30 kg	30 mg	Once daily for up to 12 weeks
Pediatric Patients 12 to 17 Years of Age		
Short-Term Treatment of Symptomatic GERD		
Nonerosive GERD	15 mg	Once daily for up to 8 weeks

Erosive Esophagitis	30 mg	Once daily for up to 8 weeks

Please refer to amoxicillin, metronidazole and clarithromycin full prescribing information for CONTRAINDICATIONS and WARNINGS, and for information regarding dosing in elderly and renally-impaired patients.

* Lansoprazole 15 mg or 30 mg once daily for 2-4 weeks depending on the severity and persistence of symptoms. Patients who do not respond after 4 weeks, or who relapse shortly afterwards, should be investigated.

** Most patients will be healed after 4 weeks; for those patients not fully healed, a further 4 weeks treatment can be given. For patients at particular risk or with ulcers that may be difficult to heal, the higher dose and/or the longer treatment duration should be used.

+ For patients who do not heal with PREVACID® FDT for 8 weeks (5-10%), it may be helpful to give an additional 8 weeks of treatment. If there is a recurrence of erosive esophagitis, an additional 8 week course of PREVACID® FDT may be considered.

*** The recommended initial dosage of PREVACID® FDT is 60 mg once daily. The dosage should be adjusted to individual patient needs and should continue for as long as clinically indicated. Dosage up to 90 mg twice daily have been administered. Daily dose of greater than 120 mg should be administered in divided doses.

7. MODE OF ADMINISTRATION

Take PREVACID® FDT before meals. Do not crush or chew PREVACID® FDT. Take PREVACID® FDT at least 30 minutes prior to sucralfate *[see INTERACTIONS WITH OTHER MEDICAMENTS]*.

Antacids may be used concomitantly with PREVACID® FDT.

Missed doses: If a dose is missed, administer as soon as possible. However, if the next scheduled dose is due, do not take the missed dose, and take the next dose on time. Do not take two doses at one time to make up for a missed dose.

PREVACID® FDT do not break or cut. Place the tablet on the tongue, allow it to disintegrate, with or without water, until the microgranules can be swallowed. Do not chew the microgranules. The tablet typically disintegrates in less than 1 minute.

Alternatively, for children or other patients who have difficulty swallowing tablets, PREVACID® FDT can be administered with water via oral syringe or NG tube as follows:

Administration with Water in an Oral Syringe

1. Place a 15 mg tablet in oral syringe and draw up approximately 4 ml of water, or place a 30 mg tablet in oral syringe and draw up approximately 10 ml of water.
2. Shake gently to allow for a quick dispersal.
3. After the tablet has dispersed, administer the contents within 15 minutes of mixing into the mouth. Do not save the water and microgranule mixture for later use.
4. Refill the syringe with approximately 2 ml (5 ml for the 30 mg tablet) of water, shake gently, and administer any remaining contents.

Administration with Water via a NG Tube (≥ 8 French)

1. Place 15 mg tablet in a catheter-tip syringe and draw up 4 ml of water, or place a 30 mg tablet in a catheter-tip syringe and draw up 10 ml of water.
2. Shake gently to allow for a quick dispersal.
3. After the tablet has dispersed, shake the catheter-tip syringe gently in order to keep the microgranules from setting, and immediately inject the mixture through the NG tube into the stomach within 15 minutes of mixing. Do not save the water and microgranule mixture for later use.
4. Refill the catheter-tip syringe with approximately 5 ml of water, shake gently, and flush the tube.

8. CONTRAINDICATION

PREVACID® FDT is contraindicated in the Patients with known hypersensitivity to any component of the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute tubulointerstitial nephritis, and urticarial.

Proton Pump Inhibitors (PPIs), including PREVACID® FDT are contraindicated with rilpivirine-containing products (see Drug Interactions).

9. WARNING AND PRECAUTION

Warning

Before using PREVACID® FDT with antibiotics to eradicate *H. pylori*, prescribers should refer to the full prescribing information of the respective antibiotic for guidance.

Precaution

Careful Administration: (PREVACID® FDT should be administered with caution to the following patients.)

1) Patients with a past history of drug hypersensitivity
2) Elderly patients (See Special Populations, Geriatric use)
3) Patients with impaired renal and hepatic function (See Special Populations, Renal Impairment, Hepatic Impairment)
4) Presence of Gastric Malignancy
   In adults, symptomatic response to therapy with PREVACID® does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing in adult patients who have a suboptimal response or an early symptomatic relapse after completing treatment with a PPI. In older patients, also consider an endoscopy.
5) Acute Tubulointerstitial Nephritis
   Acute tubulointerstitial nephritis (TIN) has been observed in patients taking PPIs and may occur at any point during PPI therapy Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function (e.g., malaise, nausea, anorexia). In reported case series, some patients were diagnosed on biopsy and in the absence of extra-renal manifestations (e.g., fever, rash or arthralgia).
   Discontinue PREVACID® and evaluate patients with suspected acute TIN.
6) *Clostridium difficile* Associated Diarrhea
   Published observational studies suggest that PPI therapy like PREVACID® may be associated with an increased risk of *Clostridium difficile*- associated diarrhea (CDAD), especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve.

   Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

   CDAD has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with PREVACID®, refer to Warnings and Precautions section of their prescribing information.

7) Bone Fracture

Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines *[see Recommended dose, Mode of administration]*.

8) Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with the use of PPIs [*see Adverse Drug Reactions*]. Discontinue PREVACID or PREVACID SoluTab at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation

9) Cutaneous and Systemic Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including lansoprazole. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE.

The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.

Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving PREVACID®, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in four to 12 weeks.
Serological testing (e.g., ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

10) Cyanocobalamin (vitamin B12) Deficiency

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 B12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed in patients treated with PREVACID®.

11) Hypomagnesemia and Mineral Metabolism

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. Hypomagnesemia may lead to hypocalcemia and/or hypokalemia and may exacerbate underlying hypocalcemia in at-risk

patients. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

Consider monitoring magnesium and calcium levels prior to initiation of PREVACID or PREVACID SoluTab and periodically while on treatment in patients with a preexisting risk of hypocalcemia (e.g., hypoparathyroidism). Supplement with magnesium and/or calcium, as necessary. If hypocalcemia is refractory to treatment, consider discontinuing the PPI.

12) Interactions with Investigations for Neuroendocrine Tumors
Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop lansoprazole treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g., for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary *[see Interaction with other medicaments].*

13) Interaction with Methotrexate
Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients *[see Interaction with other medicaments, Pharmacokinetics].*

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14) Patients with Phenylketonuria
Phenylalanine can be harmful to patients with phenylketonuria (PKU). PREVACID®FDT contains phenylalanine, a component of aspartame. Each 15 mg tablet contains 2.5 mg and each 30 mg tablet contains 5.1 mg of phenylalanine. Before prescribing PREVACID®FDT to a patient with PKU, consider the combined daily amount of phenylalanine from all sources, including PREVACID®FDT.

15) Fundic Gland Polyps
PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPI users who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

16) **Risk of Heart Valve Thickening in Pediatric Patients Less Than One Year of Age**
PREVACID and PREVACID SoluTab are not approved in pediatric patients less than one year of age. Nonclinical studies in juvenile rats with lansoprazole have demonstrated an adverse effect of heart valve thickening. The risk of heart valve injury does not appear to be relevant to patients one year of age and older *[see Use in Specific Populations*]

Special Populations

Pediatric Use

The safety and effectiveness of PREVACID® FDT have been established in pediatric patients one year to 17 years of age for short-term treatment of symptomatic GERD and erosive esophagitis.

In clinical studies of symptomatic GERD and erosive esophagitis, PREVACID was not administered beyond 12 weeks in patients one year to 11 years of age. It is not known if PREVACID is safe and effective if used longer than the recommended duration. Do not exceed the recommended dose and duration of use in pediatric patients *(see Juvenile Animal Toxicity Data).*

PREVACID was not effective in pediatric patients with symptomatic GERD one month to less than one year of age in a multicenter, double-blind, placebo - controlled study. Therefore, safety and effectiveness have not been established in patients less than one year of age. Nonclinical studies in juvenile rats have demonstrated an adverse effect of heart valve thickening and bone changes at lansoprazole doses higher than the maximum recommended equivalent human dose.

- **Neonate to less than 1 year of age**

The pharmacokinetics of lansoprazole were studied in pediatric patients with GERD aged less than 28 days and 1 to 11 months. Compared to healthy adults receiving 30 mg, neonates had higher exposure (mean weight-based normalized AUC values 2.04- and 1.88-fold higher at doses of 0.5 and 1 mg/kg/day, respectively). Infants aged ≤10 weeks had clearance and exposure values that were similar to neonates. Infants aged greater than 10 weeks who received 1 mg/kg/day had mean AUC values that were similar to adults who received a 30 mg dose.

Lansoprazole was not found to be effective in a U.S. and Polish 4 week multi-center, double-blind, placebo-controlled, parallel-group study of 162 patients between one month and less than 12 months of age with symptomatic GERD based on a medical history of crying/fussing/irritability associated with feedings who had not responded to conservative GERD management (i.e., non-pharmacologic intervention) for 7 to 14 days. Patients received lansoprazole as a suspension daily (0.2 to 0.3 mg/kg/day in infants ≤10 weeks of age or 1.0 to 1.5 mg/kg/day in infants greater than 10 weeks or placebo) for up to 4 weeks of double-blind treatment.

The primary efficacy endpoint was assessed by greater than 50% reduction from baseline in either the percent of feedings with a crying/fussing/irritability episode or the duration (minutes) of a crying/fussing/irritability episode within one hour after feeding.

There was no difference in the percentage of responders between the lansoprazole pediatric suspension group and placebo group (54% in both groups).

There were no adverse events reported in pediatric clinical studies (one month to less than 12 months of age) that were not previously observed in adults.

Based on the results of the Phase 3 efficacy study, lansoprazole was not shown to be effective. Therefore, these results do not support the use of lansoprazole in treating symptomatic GERD in infants.

- **1 year to 11 years of age**

In an uncontrolled, open label, U.S. multi-center study, 66 pediatric patients (one yearto 11 years of age) with GERD were assigned, based on body weight, to receive an initial dose of either PREVACID® FDT 15 mg q.d. if ≤ 30 kg or PREVACID® FDT 30 mg q.d. if > 30 kg administered for 8 to 12 weeks. The PREVACID® FDT dose was increased (up to 30 mg b.i.d.) in 24 of 66 pediatric patients after 2 or more weeks of treatment if they remained symptomatic. At baseline 85% of patients had mild to moderate overall GERD symptoms (assessed by investigator interview), 58% had non-erosive GERD and 42% had erosive esophagitis (assessed by endoscopy).

After 8 to 12 weeks of PREVACID® FDT treatment, the intent-to-treat analysis demonstrated an approximate 50% reduction in frequency and severity of GERD symptoms.

Twenty-one of 27 erosive esophagitis patients were healed at 8 weeks and 100% of patients were healed at 12 weeks by endoscopy.

Table 1 GERD symptoms improvement and Erosive Esophagitis healing rates in pediatric patients age 1 Year to 11 Years of Age

GERD	Final Visit[a] % (n/N)
Symptomatic GERD	
Improvement in Overall GERD Symptoms[b]	76% (47/62 [c])
Erosive Esophagitis	
Improvement in Overall GERD Symptoms[b]	81% (22/27)
Healing Rate	100% (27/27)

[a] At Week 8 or Week 12
[b] Symptoms assessed by patients diary kept by caregiver.
[c] No data were available for 4 pediatric patients

In a study of 66 pediatric patients in the age group 1 year to 11 years old after treatment with PREVACID® FDT given orally in doses of 15 mg q.d. to 30 mg b.i.d., increases in serum gastrin levels were similar to those observed in adult studies. Median fasting serum gastrin levels increased 89% from 51 pg/ml at baseline to 97 pg/ml [interquartile range (25^{th}-75^{th} percentile) of 71-130 pg/ml] at the final visit.

The most frequently reported (2 or more patients) treatment-related adverse events in patients 1 to 11 years of age (N=66) were constipation (5%) and headache (3%).

- **Twelve years to 17 years of age**

In an uncontrolled, open-label, U.S. multi-center study, 87 adolescent patients (12 years to17 years of age) with symptomatic GERD were treated with PREVACID® FDT for 8 to 12 weeks. Baseline upper endoscopies classified these patients into two groups: 64 (74%) non-erosive GERD and 23 (26%) erosive esophagitis (EE). The non-erosive GERD patients received PREVACID® FDT 15 mg q.d. for 8 weeks and the EE patients received PREVACID® FDT 30 mg q.d. for 8 to 12 weeks. At baseline, 89% of these patients had mild to moderate overall GERD symptoms (assessed by investigator interviews). During 8 weeks of PREVACID® FDT treatment,

adolescent patients experienced a 63% reduction in frequency and a 69% reduction in severity of GERD symptoms based on diary results.

Twenty-one of 22 (95.5%) adolescent erosive esophagitis patients were healed after 8 weeks of PREVACID®FDT treatment. One patient remained unhealed after 12 weeks of treatment.

Table 2 GERD symptom improvement and Erosive Esophagitis healing rates in pediatric patients age 12 years to 17 years of age

GERD	**Final Visit**% (n/N)
Symptomatic GERD (All patients)	
Improvement in Overall GERD Symptoms[a]	73.2% (60/82)[b]
Non-erosive GERD	
Improvement in Overall GERD Symptoms[a]	71.2% (42/59)[b]
Erosive Esophagitis	
Improvement in Overall GERD Symptoms[a]	78.3% (18/23)
Healing Rate[c]	95.5% (21/22)[c]

[a] Symptoms assessed by patients diary (parents/caregivers as necessary).

[b] No data available for 5 patients.

[c] Data from one healed patients were excluded from this analysis due to timing of final endoscopy.

In these 87 adolescent patients, increases in serum gastrin levels were similar to those-observed in adult studies, median fasting serum gastrin levels increased 42% from 45 pg/ml at baseline to 64 pg/ml [interquartile range (25^{th} – 75^{th} percentile) of 44 – 88 pg/ml] at the final visit. (Normal serum gastrin levels are 25 to 111 pg/ml)

The most frequently reported (at least 3%) treatment-related adverse events in these patients were headache (7%), abdominal pain (5%), nausea (3%) and dizziness (3%). Treatment-related dizziness, reported in this prescribing information as occurring in <1% of adult patients, was reported in this study by 3 adolescent patients with non-erosive GERD, who had dizziness concurrently with other events (such as migraine, dyspnea, and vomiting).

Juvenile Animal Toxicity Data
Heart Valve Thickening
In two oral toxicity studies, thickening of the mitral heart valve occurred in juvenile rats treated with lansoprazole. Heart valve thickening was observed primarily with oral dosing initiated on postnatal Day 7 (age equivalent to neonatal humans) and postnatal Day 14 (human age equivalent of approximately one year) at doses of 250 mg/kg/day and higher (at postnatal Day 7 and postnatal Day 14, respectively 6.2 times and 4.2 times the daily pediatric dose of 15 mg in pediatric patients age one to 11 years weighing 30 kg or less, based on AUC).

The treatment durations associated with heart valve thickening ranged from 5 days to 8 weeks. The findings reversed or trended towards reversibility after a 4-week drug-free recovery period. The incidence of heart valve thickening after initiation of dosing on postnatal Day 21 (human age equivalent of approximately two years) was limited to a single rat (1/24) in groups given 500 mg/kg/day for 4 or 8 weeks (approximately 5.2 times the daily pediatric dose of 15 mg in pediatric patients age one to 11 years weighing 30 kg or less, based on AUC). Based on

exposure margins, the risk of heart valve injury does not appear to be relevant to patients one year of age and older.

Bone Changes
In the eight-week oral toxicity study in juvenile rats with dosing initiated on postnatal Day 7, doses equal to or greater than 100 mg/kg/day (2.5 times the daily pediatric dose of 15 mg in children age one to 11 years weighing 30 kg or less, based on AUC) produced delayed growth, with impairment of weight gain observed as early as postnatal Day 10 (age equivalent to neonatal humans). At the end of treatment, the signs of impaired growth at 100 mg/kg/day and higher included reductions in body weight (14 to 44% compared to controls), absolute weight of multiple organs, femur weight, femur length, and crown-rump length. Femoral growth plate thickness was reduced only in males and only at the 500 mg/kg/day dose. The effects related to delayed growth persisted through the end of the four-week recovery period. Longer term data were not collected.

Geriatric Use
Of the total number of patients (n=21,486) in clinical studies of PREVACID, 16% of patients were aged 65 years and over, while 4% were 75 years and over. No overall differences in safety or effectiveness were observed between these patients and younger patients and other reported clinical experience has not identified significant differences in responses between geriatric and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic impairment
In patients with various degrees of chronic hepatic impairment the exposure to lansoprazole was increased compared to healthy subjects with normal hepatic function. No dosage adjustment for PREVACID® is necessary for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. The recommended dosage is 15 mg orally daily in patients with severe hepatic impairment (Child-Pugh Class C).

10. INTERACTIONS WITH OTHER MEDICAMENTS
Tables 2 and 3 include drugs with clinically important drug interactions and interaction with diagnostics when administered concomitantly with PREVACID® and instructions for preventing or managing them.

Consult the labeling of concomitantly used drug to obtain further information about interactions with PPIs.

Table 2. Clinically Relevant Interactions Affecting Drugs Co-Administered with PREVACID® and Interactions with Diagnostics

Antiretrovirals	
Clinical Impact:	The Effect of PPIs on antiretroviral drugs is variable. The clinical importance and the mechanisms behind these interactions are not always known. • Decreased exposure of some antiretroviral drugs (e.g., rilpivirine, atazanavir, and nelfinavir) when used concomitantly with lansoprazole may reduce antiviral effect and promote the development of drug resistance. • Increased exposures of other antiretroviral drugs (e.g.,

	saquinavir) when used concomitantly with lansoprazole may increase toxicity of the antiretroviral drugs. • There are other antiretroviral drugs which do not result in clinically relevant interactions with lansoprazole.
Intervention:	Rilpivirine-containing products: Concomitant use with PREVACID® is contraindicated (see Contraindications). See prescribing information. Atazanavir: See prescribing information for atazanavir for dosing information. Nelfinavir: Avoid concomitant use with PREVACID®. See prescribing information for nelfinavir. Saquinavir: See the prescribing information for saquinavir and monitor for potential saquinavir toxicities. Other antiretrovirals: See prescribing information
Warfarin	
Clinical Impact:	Increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death.
Intervention:	Monitor INR and prothrombin time. Dose adjustment of warfarin may be needed to maintain target INR range. See prescribing information for warfarin.
Methotrexate	
Clinical Impact:	Concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum concentrations of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. No formal drug interaction studies of high-dose methotrexate with PPIs have been conducted (see Warnings and Precautions (13)).
Intervention:	A temporary withdrawal of PREVACID® may be considered in some patients receiving high-dose methotrexate.
Digoxin	
Clinical Impact:	Potential for increased exposure of digoxin.
Intervention:	Monitor digoxin concentrations. Dose adjustment of digoxin may be needed to maintain therapeutic drug concentrations. See prescribing information for digoxin.
Theophylline	
Clinical Impact:	Increased clearance of theophylline.
Intervention:	Individual patients may require additional titration of their theophylline dosage when PREVACID® is started or stopped to ensure clinically effective blood concentrations.
Drugs Dependent on Gastric pH for Absorption (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole/itraconazole)	
Clinical Impact:	Lansoprazole can reduce the absorption of other drugs due to its effect on reducing intragastric acidity.
Intervention:	Mycophenolate mofetil (MMF): Co-administration of PPIs in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has

	not been established in transplant patients receiving PREVACID® and MMF. Use PREVACID® with caution in transplant patients receiving MMF. See the prescribing information for other drugs dependent on gastric pH for absorption.
Combination Therapy with Clarithromycin and Amoxicillin	
Clinical Impact:	Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions, including potentially fatal arrhythmias, and are contraindicated. Amoxicillin also has drug interactions.
Intervention:	• See Contraindications and Warnings and Precautions in prescribing information for clarithromycin. • See Drug Interactions in prescribing information for amoxicillin.
Tacrolimus	
Clinical Impact:	Potentially increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.
Intervention:	Monitor tacrolimus whole blood trough concentrations. Dose adjustment of tacrolimus may be needed to maintain therapeutic drug concentrations. See prescribing information for tacrolimus.
Interactions with Investigations of Neuroendocrine Tumors	
Clinical Impact:	CgA levels increase secondary to PPI-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors *(see Warnings and Precautions (12))*.
Intervention:	Temporarily stop PREVACID® treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g., for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.
Interaction with Secretin Stimulation Test	
Clinical Impact:	Hyper-response in gastrin secretion in response to secretin stimulation test, falsely suggesting gastrinoma.
Intervention:	Temporarily stop PREVACID® treatment at least 28 days before assessing to allow gastrin levels to return to baseline.
False Positive Urine Tests for THC	
Clinical Impact:	There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs.
Intervention:	An alternative confirmatory method should be considered to verify positive results.

Table 3. Clinically Relevant Interactions Affecting PREVACID® When Co-Administered with Other Drugs

CYP2C19 OR CYP3A4 Inducers	
Clinical Impact:	Decreased exposure of lansoprazole when used concomitantly with strong inducers.
Intervention:	St John's Wort, rifampin: Avoid concomitant use with PREVACID®. Ritonavir-containing products: See prescribing information

CYP2C19 or CYP3A4 Inhibitors	
Clinical Impact:	Increased exposure of lansoprazole is expected when used concomitantly with strong inhibitors.
Intervention:	Voriconazole: See prescribing information.
Sucralfate	
Clinical Impact:	Decreased and delayed absorption of lansoprazole.
Intervention:	Take PREVACID® at least 30 minutes prior to sucralfate *(see Mode of Administration)*.

11. PREGNANCY AND LACTATION

Pregnancy

Risk Summary

Available data from published observational studies overall do not indicate an association of adverse pregnancy outcomes with lansoprazole treatment (see Data).

In animal reproduction studies, oral administration of lansoprazole to rats during organogenesis through lactation at 6.4 times the maximum recommended human dose produced reductions in the offspring in femur weight, femur length, crown-rump length and growth plate thickness (males only) on postnatal Day 21 (see Data). These effects were associated with reduction in body weight gain. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

If PREVACID or PREVACID SoluTab is administered with clarithromycin, the pregnancy information for clarithromycin also applies to the combination regimen. Refer to the prescribing information for clarithromycin for more information on use in pregnancy.

Data

Human Data

Available data from published observational studies failed to demonstrate an association of adverse pregnancy-related outcomes and lansoprazole use. Methodological limitations of these observational studies cannot definitely establish or exclude any drug-associated risk during pregnancy. In a prospective study by the European Network of Teratology Information Services, outcomes from a group of 62 pregnant women administered median daily doses of 30 mg of lansoprazole were compared to a control group of 868 pregnant women who did not take any PPIs. There was no difference in the rate of major malformations between women exposed to PPIs and the control group, corresponding to a Relative Risk (RR)=1.04, [95% Confidence Interval (CI) 0.25-4.21]. In a population-based retrospective cohort study covering all live births in Denmark from 1996 to 2008, there was no significant increase in major birth defects during analysis of first trimester exposure to lansoprazole in 794 live births. A meta-analysis that compared 1,530 pregnant women exposed to PPIs in at least the first trimester with 133,410 unexposed pregnant women showed no significant increases in risk for congenital malformations or spontaneous abortion with exposure to PPIs (for major malformations Odds Ratio (OR)=1.12, [95% CI 0.86-1.45] and for spontaneous abortions OR=1.29, [95% CI 0.84-1.97]).

Animal Data

No adverse effects on embryo-fetal development occurred in studies performed in pregnant rats at oral lansoprazole doses up to 150 mg/kg/day (40 times the recommended human dose [30 mg/day] based on body surface area) administered during organogenesis and pregnant rabbits at oral lansoprazole doses up to 30 mg/kg/day (16 times the recommended human dose based on body surface area) administered during organogenesis.
A pre- and postnatal developmental toxicity study in rats with additional endpoints to evaluate bone development was performed with lansoprazole at oral doses of 10 to 100 mg/kg/day (0.7 to 6.4 times the maximum recommended human lansoprazole dose of 30 mg based on AUC [area under the plasma concentration-time curve]) administered during organogenesis through lactation. Maternal effects observed at 100 mg/kg/day (6.4 times the maximum recommended human lansoprazole dose of 30 mg based on AUC) included increased gestation period, decreased body weight gain during gestation, and decreased food consumption. The number of stillbirths was increased at this dose, which may have been secondary to maternal toxicity. Body weight of pups was reduced at 100 mg/kg/day starting on postnatal Day 11. Femur weight, femur length, and crown-rump length were reduced at 100 mg/kg/day on postnatal Day 21. Femur weight was still decreased in the 100 mg/kg/day group at age 17 to 18 weeks. Growth plate thickness was decreased in the 100 mg/kg/day males on postnatal Day 21, and was increased in the 30 and 100 mg/kg/day males at age 17 to 18 weeks. The effects on bone parameters were associated with reduction in body weight gain.

Lactation

Risk Summary

There is no information regarding the presence of lansoprazole in human milk, the effects on the breastfed infant, or the effects on milk production. However, lansoprazole and its metabolites are present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PREVACID or PREVACID SoluTab and any potential adverse effects on the breastfed child from PREVACID or PREVACID SoluTab or from the underlying maternal condition.

12. ADVERSE DRUG REACTIONS

The following serious adverse reactions are described below and elsewhere in labeling:

- Acute Tubulointerstitial Nephritis [(see Warning and Precautions (5)]
- *Clostridium difficile*-Associated Diarrhea [(see Warning and Precautions (6)]
- Bone Fracture [(see Warning and Precautions (7)]
- Severe Cutaneous Adverse Reactions *[see Warnings and Precautions (8)]*
- Cutaneous and Systemic Lupus Erythematosus [(see Warning and Precautions (9)]
- Cyanocobalamin (Vitamin B-12) Deficiency [(see Warning and Precautions (10)]
- Hypomagnesemia and Mineral Metabolism [(see Warning and Precautions (11)]
- Fundic Gland Polyps [(see Warning and Precautions (15)]

12.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Worldwide, over 10,000 patients have been treated with PREVACID® in Phase 2 or Phase 3 clinical trials involving various dosages and durations of treatment. In general, PREVACID® treatment has been well-tolerated in both short-term and long-term trials.

The following adverse reactions were reported by the treating physician to have a possible or probable relationship to drug in 1% or more of PREVACID®-treated patients and occurred at a greater rate in PREVACID®-treated patients than placebo-treated patients in *Table 4*.

Table 4 Incidence of Possibly or Probably Treatment-Related Adverse Reactions in Short-Term, Placebo-Controlled PREVACID® Studies

Body System/Adverse Reaction	PREVACID® (N= 2768) %	Placebo (N=1023) %
Body as a Whole		
Abdominal Pain	2.1	1.2
Digestive System		
Constipation	1.0	0.4
Diarrhea	3.8	2.3
Nausea	1.3	1.2

Headache was also seen at greater than 1% incidence but was more common on placebo. The incidence of diarrhea was similar between patients who received placebo and patients who received 15 and 30 mg of PREVACID®, but higher in the patients who received 60 mg of PREVACID® (2.9, 1.4, 4.2, and 7.4%, respectively).

The most commonly reported possibly or probably treatment-related adverse event during maintenance therapy was diarrhea.

In the risk reduction study of PREVACID® for NSAID-associated gastric ulcers, the incidence of diarrhea for patients treated with PREVACID®, misoprostol, and placebo was 5, 22, and 3%, respectively.

Another study for the same indication, where patients took either a COX-2 inhibitor or lansoprazole and naproxen, demonstrated that the safety profile was similar to the prior study. Additional reactions from this study not previously observed in other clinical trials with PREVACID® included contusion, duodenitis, epigastric discomfort, esophageal disorder, fatigue, hunger, hiatal hernia, hoarseness, impaired gastric emptying, metaplasia, and renal impairment.

12.2 Postmarketing Experience

Additional adverse experiences have been reported since PREVACID® has been marketed. The majority of these cases are foreign-sourced and a relationship to PREVACID® has not been established. Because these reactions were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events are listed below by COSTART body system.

Body as a Whole: anaphylactic/anaphylactoid reactions, systemic lupus erythematosus;

Digestive System: hepatotoxicity, pancreatitis, vomiting;

Hemic and Lymphatic System: agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura;

Infections and Infestations: Clostridium difficile associated diarrhea;
Metabolism and Nutritional Disorders: hypomagnesemia; hypocalcemia, hypokalemia, hyponatremia

Musculoskeletal System: bone fracture, myositis;

Skin and Appendages: severe dermatologic reactions including erythema multiforme, SJS/TEN (some fatal), DRESS, AGEP, cutaneous lupus erythematosus;

Special Senses: speech disorder;

Urogenital System: interstitial nephritis, urinary retention.

12.3 Combination Therapy with Amoxicillin and Clarithromycin
In clinical trials using combination therapy with PREVACID® plus amoxicillin and clarithromycin, and PREVACID® plus amoxicillin, no adverse reactions peculiar to these drug combinations were observed. Adverse reactions that have occurred have been limited to those that had been previously reported with PREVACID®, amoxicillin, or clarithromycin.

Triple Therapy: PREVACID®/amoxicillin/clarithromycin
The most frequently reported adverse reactions for patients who received triple therapy for 14 days were diarrhea (7%), headache (6%), and taste perversion (5%). There were no statistically significant differences in the frequency of reported adverse reactions between the 10- and 14-day triple therapy regimens. No treatment-emergent adverse reactions were observed at significantly higher rates with triple therapy than with any dual therapy regimen.

For information about adverse reactions with antibacterial agents (amoxicillin and clarithromycin) indicated in combination with PREVACID®, refer to the Undesirable Effects section of their prescribing information.

12.4 Laboratory Values
The following changes in laboratory parameters in patients who received PREVACID® were reported as adverse reactions:

Abnormal liver function tests, increased SGOT (AST), increased SGPT (ALT), increased creatinine, increased alkaline phosphatase, increased globulins, increased GGTP, increased/decreased/abnormal WBC, abnormal AG ratio, abnormal RBC, bilirubinemia, blood potassium increased, blood urea increased, crystal urine present, eosinophilia, hemoglobin decreased, hyperlipemia, increased/decreased electrolytes, increased/decreased cholesterol, increased glucocorticoids, increased LDH, increased/decreased/abnormal platelets, increased gastrin levels and positive fecal occult blood. Urine abnormalities such as albuminuria, glycosuria, and hematuria were also reported. Additional isolated laboratory abnormalities were reported.

In the placebo controlled studies, when SGOT (AST) and SGPT (ALT) were evaluated, 0.4% (4/978) and 0.4% (11/2677) patients, who received placebo and PREVACID®, respectively, had enzyme elevations greater than three times the upper limit of normal range at the final treatment visit. None of these patients who received PREVACID® reported jaundice at any time during the study.

In clinical trials using combination therapy with PREVACID® plus amoxicillin and clarithromycin, and PREVACID® plus amoxicillin, no increased laboratory abnormalities particular to these drug combinations were observed.

For information about laboratory value changes with antibacterial agents (amoxicillin and clarithromycin) indicated in combination with PREVACID®, refer to the Undesirable Effects section of their prescribing information.

13. OVERDOSE AND TREATMENT

Lansoprazole is not removed from the circulation by hemodialysis. In one reported case of overdose, the patient consumed 600 mg of lansoprazole with no adverse reaction.
Oral doses up to 5000 mg/kg in rats (approximately 1300 times the recommended human dose based on body surface area) and mice (about 675.7 times the recommended human dose based on body surface area) did not produce deaths or any clinical signs.

In the event of over-exposure, treatment should be symptomatic and supportive.

14. STORAGE CONDITION

Store below 30°C in the original packaging.

PRECAUTION FOR PREVACID® FDT

1. The tablet of PREVACID® FDT is orally dispersed, but the ingredients are not absorbed through oral mucous membrane. Therefore, this tablet should be swallowed with saliva or water after placing the tablet on the tongue.
2. This product is more fragile compared with the tablets heretofore in use.
3. Use the tablet as soon as possible after unsealing, even before the expiration date.

15. DOSAGE FORMS AND PACKAGING AVAILABLE

14 tablets per blister, 1 or 2 blisters in 1 aluminum pouch and packed 1 blister/box and 2 blisters/box (14 tablets/box and 28 tablets/box)

16. NAME AND ADDRESS OF MANUFACTURING/ MARKETING AUTHORIZATION HOLDER

Manufactured by **KOKANDO CO., LTD., Toyama, Japan** (for TAKEDA PHARMACEUTICAL COMPANY LIMITED, Osaka, Japan)
Repacked by **AUPA BIOPHARM CO., LTD, Huko/Hsin Chu Hsien, Taiwan**
Imported by **TAKEDA (THAILAND), LTD., Bangkok, Thailand**

17. DATE OF REVISION OF PACKAGE INSERT

May 2022