

## PRODUCT MONOGRAPH

### <sup>Pr</sup>Hp-PAC<sup>®</sup>

lansoprazole delayed-release capsules (manufacturer's standard), 30 mg

clarithromycin tablets, USP, film-coated, 500 mg

amoxicillin capsules, 500 mg

#### *Helicobacter pylori Eradication Therapy*

**NOTE: THESE PRODUCTS ARE INTENDED ONLY FOR USE AS DESCRIBED. THE INDIVIDUAL PRODUCTS CONTAINED IN THE Hp-PAC<sup>®</sup> SHOULD NOT BE USED ALONE OR IN COMBINATION FOR OTHER PURPOSES. THE INFORMATION DESCRIBED IN THIS PRODUCT MONOGRAPH CONCERNS ONLY THE USE OF THESE PRODUCTS AS INDICATED IN THIS DAILY ADMINISTRATION PACK. FOR INFORMATION ON THE USE OF THE INDIVIDUAL COMPONENTS WHEN DISPENSED AS INDIVIDUAL MEDICATIONS OUTSIDE THIS COMBINED USE FOR THE ERADICATION OF HELICOBACTER PYLORI (H. PYLORI), THE RESPECTIVE PRODUCT MONOGRAPHS FOR THESE PRODUCTS SHOULD BE CONSULTED.**

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## Hp-PAC<sup>®</sup>

lansoprazole delayed-release capsules, 30 mg

clarithromycin tablets, USP, film-coated, 500 mg

amoxicillin capsules, 500 mg

### PART I: HEALTH PROFESSIONAL INFORMATION

#### SUMMARY PRODUCT INFORMATION

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
oral	Lansoprazole delayed-release capsules / 30 mg	Cellulosic polymers, colloidal silicon dioxide, D&C Red No. 28, FD&C Blue No. 1, FD&C Red No. 40, gelatin, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar spheres, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide.
	Clarithromycin film-coated tablets / 500 mg	Cellulosic polymers, croscarmellose sodium, D&C Yellow No. 10, magnesium stearate, povidone, propylene glycol, silicon dioxide, sorbic acid, sorbitan monooleate, stearic acid, talc, titanium dioxide and vanillin.
	Amoxicillin capsules / 500 mg	Colloidal silicon dioxide, D&C Yellow No. 10, dry-flo starch, FD&C Blue No. 1, FD&C Red No. 3, FD&C Red No. 40, FD&C Yellow No. 6, gelatin, magnesium stearate, sodium lauryl sulfate, talc and titanium dioxide.  <i>This is a complete listing of nonmedicinal ingredients.</i>

## INDICATIONS AND CLINICAL USE

The components of the Hp-PAC<sup>®</sup> [PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)], in combination with clarithromycin film-coated tablets plus amoxicillin capsules as triple therapy, are indicated for:

- the treatment of patients with *Helicobacter pylori* (*H. pylori*) infection and active duodenal ulcer disease. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence (See **CLINICAL TRIALS** and **DOSAGE AND ADMINISTRATION**).

In patients with a recent history of duodenal ulcers who are *H. pylori* positive, eradication therapy may reduce the rate of recurrence of duodenal ulcers. The optimal timing for eradication therapy for such patients remains to be determined.

In patients who fail a therapy combination containing clarithromycin, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, an alternative therapy combination is recommended.

Resistance to amoxicillin has not been demonstrated in clinical studies with lansoprazole delayed-release capsules and amoxicillin.

Table 1 summarizes the eradication rates for the *H. pylori* Triple Therapy treatment regimen.

Treatment Regimen	Days/ Study No.	Evaluable (Per Protocol)* % (n/N)	ITT (all data)** % (n/N)	ITT (Worst Case)# % (n/N)
PREVACID <sup>®</sup> 30 mg/ Clarithromycin 500 mg/ Amoxicillin 1 g (all b.i.d.)	14 / M93-131	92 (44/48)	94 (47/50)	86 (47/55)
	14 / M95-392	86 (57/66)	87 (58/67)	83 (58/70)
PREVACID <sup>®</sup> 30 mg/ Clarithromycin 500 mg/ Amoxicillin 1 g (all b.i.d.)	10 / M95-399	84 (103/123)	86 (110/128)	81 (110/135)
PREVACID <sup>®</sup> 30 mg/ Clarithromycin 250 mg/ Amoxicillin 1 g (all b.i.d.)	7 / GB 94/110	90 (103/114)	90 (104/116)	86 (104/121)
ITT = intent-to-treat patients * Based on evaluable patients with confirmed duodenal ulcer and /or gastritis and <i>H. pylori</i> infection at baseline defined as at least two of three positive endoscopic tests from CLOtest <sup>®</sup> , histology and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy. ** Patients were included in the analysis if they had documented <i>H. pylori</i> infection at baseline as defined above and had a confirmed duodenal ulcer. # “Worst case” included patients with no available data as failures. Patients were included in the analysis if they had documented duodenal ulcer (active) and <i>H. pylori</i> infection at baseline defined as at least two of three positive endoscopic tests from CLOtest <sup>®</sup> , histology and/or culture.				

## CONTRAINDICATIONS

- Patients with known hypersensitivity to any component of the formulations of PREVACID<sup>®</sup>, any macrolide antibiotic or any penicillin. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.
- Clarithromycin is contraindicated as concurrent therapy with astemizole, terfenadine, cisapride, pimizide, ergotamine or dihydroergotamine. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with cisapride, astemizole, pimizide, or terfenadine resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to inhibition of hepatic metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported (see **DRUG INTERACTIONS**).
- Amoxicillin is contraindicated in cases where infectious mononucleosis is either suspected or confirmed.

**For information on the use of the individual components of the Hp-PAC<sup>®</sup> when dispensed as individual medications outside the combined use for the treatment of *Helicobacter pylori* (*H. pylori*), the respective Product Monographs for these products should be consulted.**

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

- Clarithromycin should not be used in pregnancy except where no alternative therapy is appropriate, particularly during the first 3 months of pregnancy. If pregnancy occurs while taking the drug, the patient should be apprised of the potential hazard to the fetus. Clarithromycin has demonstrated adverse effects on pregnancy outcome and/or embryo-fetal development in monkeys, mice, rats and rabbits at doses that produced plasma levels 2 to 17 times the serum levels obtained in humans treated at the maximum recommended doses (see WARNINGS AND PRECAUTIONS section in the Clarithromycin Product Monograph).
- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.
- There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and the appropriate therapy instituted.

*Serious anaphylactic reactions require immediate emergency treatment with epinephrine, oxygen, corticosteroids, and airway management, including intubation, as indicated.*

### General

#### ***H. pylori* Eradication and Compliance**

To avoid failure of the eradication treatment with a potential for developing antimicrobial resistance and a risk of failure with subsequent therapy, patients should be instructed to follow closely the prescribed regimen.

For the eradication of *H. pylori*, amoxicillin and clarithromycin should not be administered to patients with renal impairment since the appropriate dosage in this patient population has not yet been established.

The possibility of superinfections with fungal organisms or bacterial pathogens should be kept in mind during therapy. In such cases, discontinue Hp-PAC<sup>®</sup> and substitute appropriate treatment.

### **PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)**

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

### **BIAXIN<sup>®</sup> BID (clarithromycin tablets, USP, film-coated)**

Clarithromycin should be administered with caution to any patient who has demonstrated some form of drug allergy, particularly to structurally related-drugs. If an allergic reaction to clarithromycin occurs, administration of the drug should be discontinued. Serious hypersensitivity reactions may require epinephrine, antihistamines, or corticosteroids.

There have been postmarketing reports of colchicine toxicity with concurrent use of clarithromycin and colchicine. In patients with impaired renal function and/or who are elderly, colchicine and clarithromycin should not be used concurrently due to the risk of colchicine toxicity. Deaths have been reported in some such patients (see **Drug Interactions: Colchicine** and **ADVERSE REACTIONS**).

### **AMOXICILLIN (amoxicillin trihydrate) Capsules**

Periodic assessment of renal, hepatic and hematopoietic functions should be made during prolonged therapy with Amoxicillin (amoxicillin trihydrate).

If superinfections with mycotic or bacterial pathogens occur (usually involving *Aerobacter*, *Pseudomonas* or *Candida*) treatment with Amoxicillin should be discontinued and appropriate therapy instituted.

### **Carcinogenesis and Mutagenesis**

#### **PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)**

Safety concerns of long-term treatment relate to hypergastrinemia, possible enterochromaffin-like (ECL) effect and carcinoid formation. ECL cell hyperplasia and gastric carcinoid tumours were observed in four animal studies.

In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with doses of 5 to 150 mg/kg/day about 1 to 40 times the exposure on a body surface (mg/m<sup>2</sup>) basis, of a 50 kg person of average height (1.46 m<sup>2</sup> body surface area) given the recommended human dose of 30 mg/day (22.2 mg/m<sup>2</sup>). Lansoprazole produced dose-related gastric entero-chromaffin-like (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose related increase of testicular interstitial cell adenomas. The

incidence of these adenomas in rats receiving doses of 15 to 150 mg/kg/day (4 to 40 times the recommended human dose based on body surface area) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rats. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg/kg/day (13 times the recommended human dose based on body surface area) in a one-year toxicity study.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with doses of 15 to 600 mg/kg/day, 2 to 80 times the recommended human dose based on body surface area. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. Lansoprazole also induced a low, non-dose-related incidence of carcinoid tumours in the gastric mucosa in several dose groups (one female mouse in the 15 mg/kg/day group, one male mouse in the 150 mg/kg/day group, and 2 males and 1 female in the 300 mg/kg/day group). It also produced an increased incidence of liver tumours (hepatocellular adenoma plus carcinoma). The tumour incidences in male mice treated with 300 and 600 mg/kg/day (40 to 80 times the recommended human dose based on body surface area) and female mice treated with 150 to 600 mg/kg/day (20 to 80 times the recommended human dose based on body surface area) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg/kg/day (10 to 80 times the recommended human dose based on body surface area).

Analysis of gastric biopsy specimens from patients after short-term treatment of proton pump inhibitors have not detected ECL cell effects similar to those seen in animal studies. Longer term studies in humans revealed a slight increase in the mean ECL-cell density, although there was no microscopic evidence of cell hyperplasia. Similar results were seen in the maintenance treatment studies, where patients received up to 15 months of lansoprazole therapy. Serum gastrin values increased significantly from their baseline values but reached a plateau after two months of therapy. By one month post-treatment, fasting serum gastrin values returned to lansoprazole therapy baseline. Moreover, results from gastric biopsies from short-term, long-term and maintenance treatment studies indicate that there are no clinically meaningful effects on gastric mucosa morphology among lansoprazole-treated patients. For further details, see information under **PHARMACOLOGY** and **TOXICOLOGY**.

### **BIAXIN<sup>®</sup> BID (clarithromycin tablets, USP, film-coated)**

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of clarithromycin.

The following in vitro mutagenicity tests have been conducted with clarithromycin: Salmonella/mammalian microsome test, bacterial induced mutation frequency test, in vitro chromosome aberration test, rat hepatocyte DNA synthesis assay, mouse lymphoma assay, mouse dominant lethal study, mouse micronucleus test. All tests had negative results except the in vitro chromosome aberration test which was weakly positive in one test and negative in another. In addition, a Bacterial Reverse-Mutation Test (Ames Test) has been performed on clarithromycin metabolites with negative results.

## **AMOXICILLIN (amoxicillin trihydrate) Capsules**

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of amoxicillin. Studies to detect mutagenic potential of amoxicillin alone have not been conducted.

### **Gastrointestinal**

#### **PREVACID® (lansoprazole delayed-release capsules)**

When gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with lansoprazole delayed-release capsules is instituted as treatment with this drug may alleviate symptoms and delay diagnosis.

#### **BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents, including clarithromycin.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *C. difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug effective against *C. difficile*.

### **Genitourinary**

#### **PREVACID® (lansoprazole delayed-release capsules)**

In the 24-month toxicology study in rats, after 18 months of treatment, Leydig cell hyperplasia increased above the concurrent and historical control level at dosages of 15 mg/kg/day or higher.

Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg/kg/day (13 times the recommended human dose based on body surface area) in a one-year toxicity study.

These changes are associated with endocrine alterations which have not been, to date, observed in humans. For further details, see information under **PHARMACOLOGY** and **TOXICOLOGY**.

## **Hepatic/Biliary/Pancreatic**

### **PREVACID® (lansoprazole delayed-release capsules)**

It is recommended that the initial dosing regimen need not be altered for patients with mild or moderate liver disease, but for patients with moderate impairment, doses higher than 30 mg per day should not be administered unless there are compelling clinical indications. Dose reduction in patients with severe hepatic disease should be considered.

### **BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

Refer to **WARNINGS AND PRECAUTIONS - Renal**.

## **Immune**

### **BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

Allergic reactions (including anaphylaxis) have been reported in patients receiving clarithromycin orally.

### **AMOXICILLIN (amoxicillin trihydrate) Capsules**

A morbilliform rash following the use of ampicillin in patients with infectious mononucleosis has been well documented and has also been reported to occur following the use of amoxicillin.

## **Ophthalmologic**

### **PREVACID® (lansoprazole delayed-release capsules)**

#### *Retinal atrophy*

In animal studies, retinal atrophy was observed in rats dosed orally for 2 years with lansoprazole at doses of 15 mg/kg/day and above. These changes in rats are believed to be associated with the effects of taurine imbalance and phototoxicity in a susceptible animal model.

Clinical data available from long-term lansoprazole delayed-release capsules studies are not suggestive of any drug-induced eye toxicity in humans. In humans, there are presently no concerns for ocular safety with short-term lansoprazole treatment and the risks associated with long-term use for nearly five years appear to be negligible.

The finding of drug-induced retinal atrophy in the albino rat is considered to be species-specific with little relevance for humans. For further details, see information under **PHARMACOLOGY** and **TOXICOLOGY**.

## **Renal**

### **PREVACID® (lansoprazole delayed-release capsules)**

No dosage modification of lansoprazole is required in patients with renal insufficiency.

### **BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

Clarithromycin is principally excreted by the liver and kidney (see **DOSAGE AND ADMINISTRATION**).

For the eradication of *H. pylori*, amoxicillin and clarithromycin should not be administered to patients with renal impairment since the appropriate dosage in this patient population has not yet been established.

### **AMOXICILLIN (amoxicillin trihydrate) Capsules**

Because amoxicillin is excreted mostly by the kidney, the dosage for patients with renal impairment should be reduced in proportion to the degree of loss of renal function.

## **Sensitivity/Resistance**

### **BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

#### ***Antibiotic Resistance in Relation to H. pylori Eradication***

Three patients 3/82 (3.7%) who had isolates susceptible to clarithromycin pretreatment and were treated with the triple therapy regimen remained *H. pylori* positive posttreatment. None of the isolates from these three patients had susceptibility results available after treatment with triple therapy; therefore, it is unknown whether or not these patients developed resistance to clarithromycin. Sixteen percent of the patients treated with the dual therapy regimen developed clarithromycin resistance post-treatment. Therefore, development of clarithromycin resistance should be considered as a possible risk.

### **AMOXICILLIN (amoxicillin trihydrate) Capsules**

If superinfections with mycotic or bacterial pathogens occur (usually involving *Aerobacter*, *Pseudomonas* or *Candida*) treatment with Amoxicillin should be discontinued and appropriate therapy instituted.

## **Use in Women**

Over 4000 women were treated with lansoprazole. Ulcer healing rates in females are similar to those in males. The incidence rates of adverse events are also similar to those seen in males.

## **Special Populations**

### **Pregnant Women:**

#### **PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)**

Reproductive studies conducted in pregnant rats at oral doses up to 150 mg/kg/day (40 times the recommended human dose based on body surface area), and in rabbits at oral doses up to 30 mg/kg/day (16 times the recommended human dose based on body surface area), did not disclose any evidence of a teratogenic effect. Maternal toxicity and a significant increase in fetal mortality were observed in the rabbit study at doses above 10 mg/kg/day. In rats, maternal toxicity and a slight reduction in litter survival and weights were noted at doses above 100 mg/kg/day.

There are no adequate or well-controlled studies in pregnant women. Therefore, lansoprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### **BIAXIN<sup>®</sup> BID (clarithromycin tablets, USP, film-coated)**

There are no adequate and well-controlled studies in pregnant women. The benefits against risk, particularly during the first 3 months of pregnancy should be carefully weighed by a physician (see **WARNINGS AND PRECAUTIONS**). Four teratogenicity studies in rats (three with oral doses and one with intravenous doses up to 160 mg/kg/day administered during the period of major organogenesis) and two in rabbits (at oral doses up to 125 mg/kg/day or intravenous doses of 30 mg/kg/day administered during gestation days 6 to 18) failed to demonstrate any teratogenicity from clarithromycin. Two additional oral studies in a different rat strain at similar doses and similar conditions demonstrated a low incidence of cardiovascular anomalies at doses of 150 mg/kg/day administered during gestation days 6 to 15. Plasma levels after 150 mg/kg/day were 2 times the human serum levels.

Four studies in mice revealed a variable incidence of cleft palate following oral doses of 1000 mg/kg/day during gestation days 6 to 15. Cleft palate was also seen at 500 mg/kg/day. The 1000 mg/kg/day exposure resulted in plasma levels 17 times the human serum levels. In monkeys, an oral dose of 70 mg/kg/day produced fetal growth retardation at plasma levels that were 2 times the human serum levels.

Embryonic loss has been seen in monkeys and rabbits (see **TOXICOLOGY - Reproduction and Teratology**).

## **AMOXICILLIN (amoxicillin trihydrate) Capsules**

The safety of Amoxicillin in the treatment of infections during pregnancy has not been established. If the administration of Amoxicillin to pregnant patients is considered to be necessary, its use requires that the potential benefits be weighed against the possible hazards to the fetus.

### **Nursing Women:**

#### **PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)**

Lansoprazole or its metabolites are excreted in the milk of rats. It is not known whether lansoprazole is excreted in human milk. Because drugs are excreted in human milk, lansoprazole should not be given to nursing mothers unless its use is considered essential.

#### **BIAXIN<sup>®</sup> BID (clarithromycin tablets, USP, film-coated)**

The safety of clarithromycin for use during breast feeding of infants has not been established. Clarithromycin is excreted in human milk.

Preweaned rats, exposed indirectly via consumption of milk from dams treated with 150 mg/kg/day for 3 weeks, were not adversely affected, despite data indicating higher drug levels in milk than in plasma.

### **Pediatrics (1 to 17 years of age):**

#### **Hp-PAC<sup>®</sup> - Triple Therapy: PREVACID<sup>®</sup>/clarithromycin/amoxicillin**

The safety and effectiveness of Hp-PAC<sup>®</sup> in pediatric patients infected with *H. pylori* have not been established.

### **Geriatrics:**

#### **Hp-PAC<sup>®</sup> - Triple Therapy: PREVACID<sup>®</sup>/clarithromycin/amoxicillin**

Elderly patients may suffer from asymptomatic renal and hepatic dysfunction. Care should be taken when administering Hp-PAC<sup>®</sup> to this patient population. (See **WARNINGS AND PRECAUTIONS - Hepatic/Biliary/Pancreatic and Renal**)

### **PREVACID® (lansoprazole delayed-release capsules)**

Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. The initial dosing regimen need not be altered for elderly patients, but subsequent doses higher than 30 mg per day should not be administered unless additional gastric acid suppression is necessary.

### **BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

Dosage adjustment should be considered in elderly patients with severe renal impairment. In a steady-state study in which healthy elderly subjects (age 65 to 81 years old) were given 500 mg every 12 hours, the maximum concentrations of clarithromycin and 14-OH clarithromycin were increased. The AUC was also increased. These changes in pharmacokinetics parallel known age-related decreases in renal function. In clinical trials, elderly patients did not have an increased incidence of adverse events when compared to younger patients.

### **AMOXICILLIN (amoxicillin trihydrate) Capsules**

There are no known specific precautions for the use of amoxicillin in the elderly.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

#### **Hp-PAC® - Triple Therapy: PREVACID®/clarithromycin/amoxicillin**

The most frequently reported ( $\geq 3\%$ ) adverse events for patients who received triple therapy were diarrhea (7%), headache (6%), and taste perversion (5%).

### **PREVACID® (lansoprazole delayed-release capsules)**

Worldwide, over 7000 patients have been treated with PREVACID® (lansoprazole) Delayed-Release Capsules during Phase II-III short-term and long-term clinical trials involving various dosages and duration of treatment. In general, lansoprazole treatment has been well tolerated.

### **BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

The majority of side effects observed in clinical trials involving 3563 patients treated with BIAXIN® BID were of a mild and transient nature. Fewer than 3% of adult patients without mycobacterial infections discontinued therapy because of drug-related side-effects. The most common drug-related adverse reactions in adults taking BIAXIN® BID were nausea, diarrhea, abdominal pain, dyspepsia, headache, taste perversion and vomiting.

## **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

### **Hp-PAC<sup>®</sup> - Triple Therapy: PREVACID<sup>®</sup>/clarithromycin/amoxicillin**

Patients in the 7-day triple therapy regimen reported fewer adverse events than those in the 10 and/or 14-day triple therapy regimens. There were no statistically significant differences in the frequency of reported adverse events between the 10- and 14-day triple therapy regimens. No treatment-emergent adverse events were observed at significantly higher rates with triple therapy than with any dual therapy regimen.

### **Combination Therapy with Clarithromycin and Amoxicillin**

In clinical trials using combination therapy with PREVACID<sup>®</sup> plus clarithromycin and amoxicillin, no adverse reactions related to these drug combinations were observed. Adverse reactions that have occurred have been limited to those that have been previously reported with PREVACID<sup>®</sup>, clarithromycin, or amoxicillin.

For more information on adverse reactions with lansoprazole, clarithromycin or amoxicillin, refer to their respective Product Monographs, under the **ADVERSE REACTIONS** section.

### **PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)**

The following adverse events were reported to have a possible or probable relationship to drug as described by the treating physician in 1% or more of lansoprazole delayed-release capsules-treated patients who participated in placebo- and positive-controlled trials (**Tables 2 and 3**, respectively). Numbers in parentheses indicate the percentage of the adverse events reported.

<b>Table 2</b> <b>Incidence of Possibly or Probably Treatment-Related Adverse Events in Short-Term, Placebo-Controlled Studies in Takeda<sup>†</sup> Safety Database</b>		
<b>Body System / Adverse Event*</b>	<b>PREVACID<sup>®@</sup></b> <b>(N=817), N (%)</b>	<b>Placebo</b> <b>(N=254), N (%)</b>
<b><i>Body as a Whole</i></b>		
Headache	63 (7.7)	31 (12.2)
Abdominal Pain	19 (2.3)	3 (1.2)
<b><i>Digestive System</i></b>		
Diarrhea	29 (3.5)	6 (2.4)
Nausea	9 (1.1)	5 (2.0)
Vomiting	7 (0.9)	3 (1.2)
Liver Function Tests Abnormal	2 (0.2)	3 (1.2)
<b><i>Nervous System</i></b>		
Dizziness	8 (1.0)	2 (0.8)
<sup>†</sup> Takeda Pharmaceuticals America, Inc. <sup>*</sup> Events reported by at least 1% of patients on either treatment are included <sup>@</sup> Doses 15 mg, 30 mg and 60 mg q.d. for 4-8 weeks		

In the Takeda Safety Database, all short-term, Phase II/III studies, one or more treatment-emergent AEs were reported by 715/1359 (52.6%) PREVACID<sup>®</sup>-treated patients; of those considered to be possibly or probably treatment-related AEs, one or more were reported by 276/1359 (20.3%) PREVACID<sup>®</sup>-treated patients. In all short-term, Phase II/III studies, one or more treatment-emergent AEs were reported by 150/254 (59.1%) placebo-treated patients; of those considered to be possibly or probably treatment-related AEs, one or more were reported by 56/254 (22.0%).

The most frequent AEs reported in the European short-term studies were diarrhea (3.3%), laboratory test abnormal (2.3%), headache (1.5%), constipation (1.2%), asthenia (1.1%), dizziness (1.1%), and abdominal pain (1.0%). The most frequent AEs reported in the Asian short-term studies were unspecified laboratory test abnormalities (7.3%), eosinophilia (1.0%), and increased SGPT (1.0%).

<b>Table 3 Incidence of Possibly or Probably Treatment-Related Adverse Events in Short-Term, Positive-Controlled Studies in Takeda<sup>†</sup> Safety Database</b>		
<b>Body System / Adverse Event*</b>	<b>PREVACID<sup>®@</sup> (N=647), N (%)</b>	<b>Ranitidine (N=393), N (%)</b>
<b><i>Body as a Whole</i></b>		
Headache	26 (4.0)	14 (3.6)
Abdominal Pain	8 (1.2)	3 (0.8)
<b><i>Digestive System</i></b>		
Diarrhea	27 (4.2)	8 (2.0)
Nausea	7 (1.1)	4 (1.0)
<b><i>Nervous System</i></b>		
Dizziness	8 (1.2)	3 (0.8)
<b><i>Skin and Appendages</i></b>		
Rash	7 (1.1)	1 (0.3)
<sup>†</sup> Takeda Pharmaceuticals America, Inc. <sup>*</sup> Events reported by at least 1% of patients on either treatment are included <sup>@</sup> Doses 15 mg, 30 mg and 60 mg q.d. for 4-8 weeks		

### **Less Common Clinical Trial Adverse Drug Reactions**

#### **Hp-PAC<sup>®</sup> - Triple Therapy: PREVACID<sup>®</sup>/clarithromycin/amoxicillin**

The additional adverse reactions which were reported as possibly or probably related to treatment (< 3%) in clinical trials when all three components of this therapy were given concomitantly are listed below and divided by body system:

Body as a Whole: abdominal pain;

Digestive System: dark stools, dry mouth/thirst, glossitis, rectal itching, nausea, oral moniliasis, stomatitis, tongue discoloration, tongue disorder, vomiting;

Musculoskeletal System: myalgia;

Nervous System: confusion, dizziness;

Respiratory System: respiratory disorders;

Skin and Appendages: skin reactions;

Urogenital System: vaginitis, vaginal moniliasis.

## **PREVACID® (lansoprazole delayed-release capsules)**

Additional adverse experiences occurring in <1% of patients or subjects in domestic and/or international trials, or occurring since the drug was marketed, are shown below within each body system.

Body as a Whole: asthenia, candidiasis, chest pain (not otherwise specified), edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise, carcinoma, general pain;

Cardiovascular System: angina, cerebrovascular accident, hypertension/hypotension, myocardial infarction, palpitations, shock (circulatory failure), vasodilation;

Digestive System: melena, cholelithiasis, abnormal stools/melena, bezoar, constipation, dry mouth/thirst, flatulence, gastroenteritis, gastrointestinal hemorrhage, hematemesis, anorexia, increased appetite, increased salivation, rectal hemorrhage, cardiospasm, dyspepsia, dysphagia, eructation, esophageal stenosis, esophageal ulcer, esophagitis, stomatitis, fecal discoloration, tenesmus, ulcerative colitis, gastric nodules/fundic gland polyps, carcinoid;

Endocrine System: diabetes mellitus, goiter, hyperglycemia/hypoglycemia;

Hematologic and Lymphatic System\*: agranulocytosis, anemia, aplastic anemia, hemolysis, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura;

Metabolic and Nutritional Disorders: gout, weight gain/loss, edema;

Musculoskeletal System: arthritis/arthralgia, musculoskeletal pain, myalgia;

Nervous System: agitation, amnesia, apathy, confusion, dizziness, syncope, hallucinations, hostility aggravated, libido decreased, depression, hemiplegia, insomnia, somnolence, thinking abnormality, anxiety, nervousness, paresthesia;

Respiratory System: asthma, bronchitis, cough increased, dyspnea, hemoptysis, hiccup, upper respiratory inflammation/infection, pneumonia, epistaxis;

Skin and Appendages: acne, pruritus, rash, urticaria, alopecia;

Special Senses: blurred vision, eye pain, visual field defect, tinnitus, ophthalmologic disorders, ear disorder, deafness, otitis media, taste perversion;

Urogenital System: abnormal menses, albuminuria, breast enlargement/ gynecomastia, breast tenderness, glycosuria, impotence, kidney calculus, hematuria, urinary urgency.

\* The majority of hematologic cases received were foreign-sourced and their relationship to lansoprazole was unclear.

**BIAXIN<sup>®</sup> BID (clarithromycin tablets, USP, film-coated)**

The following adverse reactions from the clarithromycin Product Monograph are provided for information:

The majority of side effects observed in clinical trials involving 3563 patients treated with BIAXIN BID<sup>®</sup> were of a mild and transient nature. Fewer than 3% of adult patients without mycobacterial infections discontinued therapy because of drug related side-effects.

The following adverse reactions were reported during these clinical studies or during post-marketing surveillance:

Body as a Whole: headache (2%), asthenia, infection, back pain, pain and chest pain.

Cardiovascular System: As with other macrolides, QT prolongation, ventricular tachycardia, and torsades de pointes have rarely been reported with clarithromycin.

Digestive System: nausea (4%), diarrhea (3%), abdominal pain (2%), dyspepsia (2%), vomiting (1%), constipation, flatulence, dry mouth, glossitis, stomatitis, gastrointestinal disorder, anorexia, oral moniliasis, tongue discoloration, hepatomegaly and pseudomembranous colitis. There have been reports of tooth discoloration in patients treated with BIAXIN BID<sup>®</sup>. Tooth discoloration is usually reversible with professional dental cleaning.

As with other macrolides, hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with BIAXIN BID<sup>®</sup>. This hepatic dysfunction may be severe and is usually reversible. In very rare instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications.

Metabolic: There have been rare reports of hypoglycemia, some of which have occurred in patients on concomitant oral hypoglycemic agents or insulin.

Nervous System: dizziness, vertigo, tinnitus, nervousness, anxiety, insomnia, nightmares, somnolence, depression, confusion, disorientation, depersonalization, hallucinations and psychosis.

Respiratory System: rhinitis, cough increased, dyspnea, pharyngitis and asthma.

Skin and Appendages: pruritus, rash, sweating; allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis and Stevens-Johnson Syndrome have occurred with orally administered clarithromycin.

Special Senses: taste perversion (2%), ear disorder, abnormal vision and conjunctivitis. There have been reports of hearing loss with clarithromycin which is usually reversible upon withdrawal of therapy. Reports of alteration of the sense of smell, usually in conjunction with taste perversion or taste loss have also been reported.

Urogenital System: hematuria, vaginal moniliasis, vaginitis and dysmenorrhea.

Hemic and Lymphatic System: eosinophilia, anemia, leukopenia and thrombocytopenia. Isolated cases of thrombocytopenia have been reported.

#### Others

Central nervous system side effects (including seizures) have been occasionally reported with erythromycin, another macrolide.

In studies of adults with pneumonia comparing clarithromycin to erythromycin base or erythromycin stearate, there were significantly fewer adverse events involving the digestive system in patients treated with clarithromycin.

### **AMOXICILLIN (amoxicillin trihydrate) Capsules**

As with other penicillins, it may be expected that untoward reactions will be related to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and cephalosporins and in those with a history of allergy, asthma, hay fever or urticaria.

The following adverse reactions have been reported as associated with the use of Amoxicillin.

Gastrointestinal:           nausea, vomiting and diarrhea.

Hypersensitivity  
Reactions:

Skin rashes and urticaria have been reported frequently. A few cases of exfoliative dermatitis and erythema multiforme have been reported. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form.

**NOTE:**

Urticaria, other skin rashes, and serum sickness–like reactions may be controlled with antihistamines and if necessary, systemic corticosteroids. Whenever such reactions occur, Amoxicillin (amoxicillin trihydrate) should be discontinued unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to amoxicillin therapy. Serious anaphylactic reactions require the immediate use of epinephrine, oxygen and intravenous steroids.

Liver:

A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants, but the significance of this finding is not known. Transient increases in serum alkaline phosphatase and lactic dehydrogenase levels have also been observed but they returned to normal on discontinuation of amoxicillin.

Hematologic and  
Lymphatic System:

anemia thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, neutropenia and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be a hypersensitivity phenomena.

Digestive System:

glossitis, black "hairy" tongue and stomatitis.

Nervous System:

As with other penicillins, acute and chronic toxicity is not a clinical problem. At extremely high doses, convulsions can occur. When penicillin reaches a high concentration in the cerebrospinal fluid, neurotoxic symptoms consisting of myoclonia, convulsive seizures and depressed consciousness may occur. Unless administration of the drug is stopped or its dosage reduced, the syndrome may progress to coma and death. Although penicillins do not normally cross the blood–brain barrier to any substantial extent, if massive doses are given (several grams per day) to elderly patients, patients with inflamed meninges or patients with impaired renal function, the above toxic reactions are likely to occur.

## **Abnormal Hematologic and Clinical Chemistry Findings**

### **PREVACID® (lansoprazole delayed-release capsules)**

In addition, the following changes in laboratory parameters were reported as adverse events. Abnormal liver function tests, increased SGOT (AST), increased SGPT (ALT), increased creatinine, increased alkaline phosphatase, increased gamma globulins, increased GGTP, increased/decreased/abnormal WBC, abnormal AG ratio, abnormal RBC, bilirubinemia, eosinophilia, hyperlipemia, increased/decreased electrolytes, increased/decreased cholesterol, increased glucocorticoids, increased LDH, increased/decreased/abnormal platelets, and increased gastrin levels. 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) placebo patients and 0.3% (11/2677) lansoprazole patients had enzyme elevations greater than three times the upper limit of normal range at the final treatment visit. None of these lansoprazole patients reported jaundice at any time during the study.

For more information on laboratory value changes with clarithromycin or amoxicillin, refer to their respective Product Monographs, under the **ADVERSE REACTIONS** section.

### **BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

In addition, changes in laboratory values with possible clinical significance were as follows:

Hepatic: elevated ALT <1%, AST <1%, GGT <1%, alkaline phosphatase <1%, LDH <1% and total bilirubin <1%.

Hematologic: decreased WBC < 1% and elevated prothrombin time (1%).

Renal: elevated BUN (4%) and elevated serum creatinine < 1%.

### **Post-Market Adverse Drug Reactions**

These events were reported during postmarketing surveillance. Estimates of frequency cannot be made since such events are reported voluntarily from a population of unknown size. Due to the uncontrolled nature of spontaneous reports, a clear causal relationship to lansoprazole cannot be established.

## **PREVACID® (lansoprazole delayed-release capsules)**

Body as a Whole - hypersensitivity reactions, including anaphylaxis; Digestive System – colitis, hepatotoxicity, pancreatitis, vomiting; Hematologic and Lymphatic System - agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura; Musculoskeletal System - myositis; Skin and Appendages - severe dermatologic reactions including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal); Special Senses - speech disorder; Urogenital System - urinary retention, interstitial nephritis.

In an estimated exposure of 240 million patients worldwide (in both postmarketing surveillance and the clinical trials), the most commonly reported ophthalmic adverse events are amblyopia (13) and vision blurred (67) according to the MedDRA terminology. All the 13 cases of amblyopia had the reported term/verbatim "blurred or smeary vision". Only two of these 13 reports were considered serious, and both are foreign-sourced reports with very little information provided. Among the 67 reports with the "vision blurred," 10 were considered serious and might be related to optic neuritis/neuropathy, whether or not believed related to the drug. In two of these ten cases, one of the examining ophthalmologists proposed a diagnosis of AION. Eight out of the ten cases were foreign-sourced. Only two US-sourced serious cases involved the report of blurred vision. Both were consumer reports without any detailed information. No physician assessed any causality in either case.

## **BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

The following list of adverse events is a compilation of adverse reactions from Postmarketing Surveillance and Postmarketing Clinical Studies for all clarithromycin formulations.

<b>System Organ Class</b>	<b>Adverse Event</b>
Blood and lymphatic system disorders	Leukopenia
	Thrombocytopenia
Investigations Cardiac disorders	Electrocardiogram QT prolonged
	Ventricular tachycardia
	Torsades de pointes
Gastrointestinal disorders	Dyspepsia
	Vomiting
	Glossitis
	Stomatitis
Infections and infestations	Candidiasis
Gastrointestinal disorders	Tongue discolouration
	Tooth discolouration
	Pancreatitis
Hepatobiliary disorders	Hepatic function abnormal

**Table 4  
Clarithromycin Post-Market Adverse Drug Reactions**

<b>System Organ Class</b>	<b>Adverse Event</b>
	Hepatitis
	Hepatitis cholestatic
	Hepatic failure
	Jaundice
Investigations	Increased liver enzymes
Metabolism and nutrition disorders	Hypoglycemia
Nervous system disorders	Dizziness
	Vertigo
	Alteration of sense of smell
	Convulsions
Psychiatric disorders	Anxiety
	Insomnia
	Bad dreams
	Confusion
	Disorientation
	Hallucination
	Psychosis
Depersonalization	
Skin and subcutaneous tissue disorders	Urticaria
	Mild skin eruptions
	Stevens Johnson syndrome
	Toxic epidermal necrosis
Immune system disorders	Anaphylaxis
Ear and labyrinth disorders	Tinnitus
	Hearing loss
Renal and urinary disorders	Interstitial nephritis

## DRUG INTERACTIONS

### Serious Drug Interactions

- Concomitant administration of clarithromycin with astemizole, cisapride, pimozide, terfenadine, ergotamine, or dihydroergotamine is contraindicated (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**).
- Clarithromycin is an inhibitor of CYP3A4. The concomitant administration of clarithromycin and drugs metabolized by this enzyme (or enzyme system) may lead to an increase in the plasma concentrations of the co-administered drug which could result in clinically significant safety concerns.

### Overview

#### **PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)**

Lansoprazole is metabolized through the cytochrome P450 system, specifically through CYP3A and CYP2C19. 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, acetylsalicylic acid, ibuprofen, phenytoin, prednisone, antacids (Maalox<sup>®</sup> and Riopan<sup>®</sup>), diazepam, clarithromycin, propranolol, amoxicillin or terfenadine in healthy subjects. These compounds are metabolized through various cytochrome P450 isozymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A.

Lansoprazole causes a profound and long lasting inhibition of gastric acid secretion; therefore, it is theoretically possible that lansoprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, digoxin). Lansoprazole substantially decreases the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, lansoprazole should not be co-administered with atazanavir. This appears to be a class effect. It is theoretically possible that lansoprazole may also interfere with the absorption of other drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, digoxin).

In a study of healthy subjects neither the pharmacokinetics of warfarin enantiomers nor prothrombin time were affected following single or multiple 60 mg doses of lansoprazole. However, there have been reports of increased International Normalized Ratio (INR) and prothrombin time in patients receiving proton pump inhibitors, including lansoprazole, 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 may need to be monitored for increases in INR and prothrombin time.

## **BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

Many categories of drugs are metabolized by the cytochrome P450 3A4 enzyme located in the liver and in the intestine. Some drugs inhibit and others induce this enzyme. Co-administration of such drugs may impact upon each other's metabolism. In some cases serum concentration may be increased and in others decreased. Care must therefore be exercised when co-administering such drugs.

Clarithromycin is reported to be an inhibitor of the enzyme P450 3A4. This may lead to increased or prolonged serum levels of those drugs also metabolized by the enzyme when co-administered with clarithromycin. For such drugs the monitoring of their serum concentrations may be necessary.

### **Drug-Drug Interactions**

#### **PREVACID® (lansoprazole delayed-release capsules)**

When lansoprazole was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of theophylline was seen, which is unlikely to be of clinical concern. Nonetheless, individual patients may require adjustment of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels.

In a single-dose crossover study when 30 mg of lansoprazole was administered concomitantly with one gram of sucralfate in healthy volunteers, absorption of lansoprazole was delayed and its bioavailability was reduced. The value of lansoprazole AUC was reduced by 17% and that for  $C_{max}$  was reduced by 21%.

In a similar study when 30 mg of lansoprazole was administered concomitantly with 2 grams of sucralfate, lansoprazole AUC and  $C_{max}$  were reduced by 32% and 55%, respectively. When lansoprazole dosing occurred 30 minutes prior to sucralfate administration,  $C_{max}$  was reduced by only 28% and there was no statistically significant difference in lansoprazole AUC. Therefore, lansoprazole may be given concomitantly with antacids but should be administered at least 30 minutes prior to sucralfate.

#### **BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

Some of the drug-drug interactions which have been reported between clarithromycin-macrolides and other drugs or drug categories are listed in **Table 5**. Like clarithromycin and omeprazole, most of the following drugs are metabolized by the P450 3A4 enzyme system.

Additional mechanisms, such as effects upon absorption, may also be responsible for interaction between drugs, including digoxin and clarithromycin.

The drugs listed in this table are based on either drug interactions case reports, clinical trials, or potential interactions due to the expected mechanism of the interaction.

<b>Table 5</b>			
<b>Established or Potential Drug-Drug Interactions</b>			
<b>Clarithromycin</b>	<b>Ref.</b>	<b>Effect</b>	<b>Clinical Comments</b>
Astemizole / Terfenadine	CT	terfenadine-acid metabolite concentrations increase  ↑ QT interval	Macrolides have been reported to alter the metabolism of terfenadine resulting in increased serum levels of terfenadine which has occasionally been associated with cardiac arrhythmias such as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsade de pointes (see <b>CONTRAINDICATIONS</b> ).  In a study involving 14 healthy volunteers, the concomitant administration of BIAXIN® BID tablets and terfenadine resulted in a two to three-fold increase in the serum levels of the acid metabolite of terfenadine, MDL 16, 455, and in prolongation of the QT interval. Similar effects have been observed with concomitant administration of astemizole and other macrolides.
Carbamazepine	C	↑ levels of carbamazepine	Clarithromycin administration in patients receiving carbamazepine has been reported to cause increased levels of carbamazepine. Blood level monitoring of carbamazepine may be considered.
Cisapride / Pimozide	C	↑ levels of cisapride ↑ levels of pimozide	Elevated cisapride levels have been reported in patients receiving clarithromycin and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsade de pointes. Similar effects have been observed in patients taking clarithromycin and pimozide concomitantly (see <b>CONTRAINDICATIONS</b> ).
Colchicine	C	Potential colchicines toxicity	Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity (see <b>PRECAUTIONS: General</b> and <b>ADVERSE REACTIONS</b> ).

<b>Table 5</b> <b>Established or Potential Drug-Drug Interactions</b>			
<b>Clarithromycin</b>	<b>Ref.</b>	<b>Effect</b>	<b>Clinical Comments</b>
Cyclosporine	C	↑ levels of cyclosporine	There have been reports of elevated cyclosporine serum concentrations when clarithromycin and cyclosporine are used concurrently. Cyclosporine levels should be monitored and the dosage should be adjusted as necessary. Patients should also be monitored for increased cyclosporine toxicity.
Didanosine	CT	No change in didanosine pharmacokinetics in HIV-infected patients (n=12)	Simultaneous administration of BIAXIN <sup>®</sup> BID tablets and didanosine to 12 HIV-infected adult patients resulted in no statistically significant change in didanosine pharmacokinetics.
Digoxin	C	↑ levels of digoxin	Elevated digoxin serum concentrations have been reported in patients receiving BIAXIN <sup>®</sup> BID tablets and digoxin concomitantly.  In post-marketing surveillance some patients have shown clinical signs consistent with digoxin toxicity, including arrhythmias. Serum digoxin levels should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.
Disopyramide / Quinidine	C	↑ levels of disopyramide, resulting ventr. Fibrillation & QT prolongation (rarely reported)  Torsades de pointes	Increased disopyramide plasma levels, resulting in ventricular fibrillation and QT prolongation, coincident with the co-administration of disopyramide and clarithromycin has rarely been reported.  There have been postmarketed reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide.  Serum levels of these medications should be monitored during clarithromycin therapy.
Ergotamine / Dihydroergotamine	C	Potential ischemic reactions  Potential ergot toxicity	There are reports that ischemic reactions may occur when clarithromycin is given concurrently with ergotamine-containing drugs.  Concurrent use of clarithromycin and ergot alkaloids has been associated in some patients with acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia. (see <b>CONTRAINDICATIONS</b> )

<b>Table 5</b> <b>Established or Potential Drug-Drug Interactions</b>			
<b>Clarithromycin</b>	<b>Ref.</b>	<b>Effect</b>	<b>Clinical Comments</b>
Fluconazole	CT	↑ clarithromycin C <sub>min</sub> & AUC	<p>Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers led to increases in the mean steady-state clarithromycin C<sub>min</sub> and AUC of 33% and 18%, respectively.</p> <p>Steady-state concentrations of 14-OH clarithromycin were not significantly affected by concomitant administration of fluconazole.</p>
Lansoprazole / Omeprazole	CT	<p>Mild change of lansoprazole and 14-OH clarithromycin concentrations</p> <p>↑ omeprazole C<sub>max</sub> &amp; AUC<sub>0-24</sub></p> <p>↑ levels of clarithromycin</p>	<p>One study demonstrated that concomitant administration of clarithromycin and lansoprazole resulted in mild changes of serum concentrations of lansoprazole and 14-OH clarithromycin. However, no dosage adjustment is considered necessary based on these data.</p> <p>Clarithromycin 500 mg t.i.d. was given in combination with omeprazole 40 mg q.d. to healthy subjects. The steady-state plasma concentrations of omeprazole were increased (i.e., C<sub>max</sub>, AUC<sub>0-24</sub>, and t<sub>1/2</sub> increased by 30%, 89%, and 34%, respectively), by concomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when co-administered with clarithromycin.</p> <p>To a lesser extent, omeprazole administration increases the serum concentrations of clarithromycin. Omeprazole administration also increases tissue and mucus concentrations of clarithromycin.</p>
Lovastatin / Simvastatin	C	Rhabdomyolysis (rarely reported)	Rhabdomyolysis coincident with the co-administration of clarithromycin and the HMG-CoA reductase inhibitors, lovastatin and simvastatin, has rarely been reported.
Atorvastatin	C		Concurrent use of atorvastatin and clarithromycin may result in increased atorvastatin exposure and an increased risk of rhabdomyolysis.
Midazolam / Triazolam	C	↓ clearance of midazolam & triazolam	Clarithromycin has been reported to decrease the clearance of midazolam and triazolam and thus may increase the pharmacologic effect of these drugs.

<b>Table 5</b>			
<b>Established or Potential Drug-Drug Interactions</b>			
<b>Clarithromycin</b>	<b>Ref.</b>	<b>Effect</b>	<b>Clinical Comments</b>
Rifabutin / Rifampin	C	↓ levels of clarithromycin  ↑ levels of rifabutin	Co-administration of rifabutin or rifampin and clarithromycin has resulted in decreased clarithromycin concentrations.  Clarithromycin has been reported to increase serum and tissue concentration of rifabutin and thus may increase the risk of toxicity.
Ritonavir / Indinavir	CT	↑ clarithromycin $C_{max}$ , $C_{min}$ & AUC          ↑ indinavir AUC ↑ clarithromycin AUC	A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg q8h and clarithromycin 500 mg q12h resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin $C_{max}$ increased by 31%, $C_{min}$ increased 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-[R]-hydroxy-clarithromycin was noted. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with CLCR 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with CLCR <30 mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1gm/day should not be coadministered with ritonavir.  One study demonstrated that the concomitant administration of clarithromycin and indinavir resulted in a metabolic interaction; the clarithromycin AUC increased by 53% and the indinavir AUC was increased by 20%, but the individual variation was large. No dose adjustment is necessary with normal renal function.
Tacrolimus	P	Potential ↑ in tacrolimus concentrations	Concomitant administration of tacrolimus and clarithromycin may result in increased plasma levels of tacrolimus and increased risk of toxicity.

<b>Table 5</b> <b>Established or Potential Drug-Drug Interactions</b>			
<b>Clarithromycin</b>	<b>Ref.</b>	<b>Effect</b>	<b>Clinical Comments</b>
Theophylline	P	Potential ↑ in theophylline concentrations	<p>Clarithromycin use in patients who are receiving theophylline may be associated with an increase of serum theophylline concentrations.</p> <p>Monitoring of serum theophylline concentrations should be considered for patients receiving high doses of theophylline or with baseline concentrations in the upper therapeutic range.</p>
Warfarin / Acenocoumarol	C	↑ anticoagulant effect	<p>There have been reports of increased anticoagulant effect when clarithromycin and oral anticoagulants are used concurrently. Anticoagulant parameters should be closely monitored. Adjustment of the anticoagulant dose may be necessary.</p> <p>Clarithromycin has also been reported to increase the anticoagulant effect of acenocoumarol.</p>
Zidovudine	C	Potential ↓ in zidovudine concentrations	<p>Simultaneous oral administration of BIAXIN® BID tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, therefore this interaction can be largely avoided by staggering the doses of clarithromycin and zidovudine.</p>
Others / Drugs metabolized by Cytochrome P <sub>450</sub> system	C/P	Potential change in serum concentration	<p>Interactions with erythromycin and/or clarithromycin have been reported with a number of other drugs metabolized by the cytochrome P<sub>450</sub> system, such as alfentanil, alprazolam, bromocriptine, cilostazol, hexobarbital, methylprednisolone, phenytoin, sildenafil, valproate or vinblastine.</p> <p>Serum concentrations of drugs metabolized by the cytochrome P<sub>450</sub> system should be monitored closely in patients concurrently receiving erythromycin or clarithromycin.</p>
<p>Legend: C = Case Study; CT = Clinical Trial; P = Potential Interactions with other drugs have not been established</p>			

## **Drug-Food Interactions**

### **PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)**

Food reduces the peak concentration and the extent of absorption of lansoprazole by about 50% to 70%. Therefore, it is recommended that lansoprazole delayed-release capsules be administered in the morning prior to breakfast and another meal.

### **BIAXIN<sup>®</sup> BID (clarithromycin tablets, USP, film-coated)**

BIAXIN<sup>®</sup> BID (clarithromycin tablets, USP, film-coated) may be given with or without meals.

## **Drug-Herb Interactions**

*Interactions with herbal products have not been established.*

## **Drug-Laboratory Interactions**

*Interactions with laboratory tests have not been established.*

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

#### **PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)**

It is recommended that the initial dosing regimen need not be altered for patients with mild or moderate liver disease, but for patients with moderate impairment, doses higher than 30 mg per day should not be administered unless there are compelling clinical indications. (See **WARNINGS AND PRECAUTIONS - Hepatic/Biliary/Pancreatic and Renal**)

#### **BIAXIN<sup>®</sup> BID (clarithromycin tablets, USP, film-coated)**

For the eradication of *H. pylori*, amoxicillin and clarithromycin should not be administered to patients with renal impairment since the appropriate dosage in this patient population has not yet been established.

## **Recommended Dose and Dosage Adjustment**

### ***Helicobacter pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence***

#### **Hp-PAC<sup>®</sup> - Triple Therapy: PREVACID<sup>®</sup>/clarithromycin/amoxicillin**

The recommended adult oral dose is 30 mg lansoprazole, 500 mg clarithromycin, and 1 g amoxicillin, all given twice daily for 7, 10 or 14 days (see **INDICATIONS AND CLINICAL USE**). Daily doses should be taken before meals.

#### **PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)**

PREVACID<sup>®</sup> (lansoprazole delayed-release capsules) should be taken daily before breakfast. Where the product may be used twice daily, it should be taken prior to breakfast and another meal. PREVACID<sup>®</sup> delayed-release capsules **SHOULD NOT BE CRUSHED OR CHEWED**.

#### **Patients with Hepatic Impairment**

The daily dose of lansoprazole should not exceed 30 mg (see **WARNINGS AND PRECAUTIONS**).

Clarithromycin may be administered without dosage adjustment in the presence of hepatic impairment if there is normal renal function.

#### **Patients with Renal Impairment**

#### **PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)**

No dosage modification of lansoprazole is necessary (see **WARNINGS AND PRECAUTIONS**).

#### **BIAXIN<sup>®</sup> BID (clarithromycin tablets, USP, film-coated)**

Refer to **WARNINGS AND PRECAUTIONS - Renal**.

#### **Elderly Patients**

The daily dose of lansoprazole should not exceed 30 mg (see **WARNINGS AND PRECAUTIONS**).

### Concomitant Antacid Use

Simultaneous administration of lansoprazole with Maalox<sup>®</sup> (aluminum and magnesium hydroxide) or Riopan<sup>®</sup> (magaldrate) results in lower peak plasma levels, but does not significantly reduce bioavailability. Antacids may be used concomitantly if required. If sucralfate is to be given concomitantly, lansoprazole should be administered at least 30 minutes prior to sucralfate (see **ACTIONS AND CLINICAL PHARMACOLOGY; Absorption with Antacids**). In clinical trials, antacids were administered concomitantly with lansoprazole delayed-release capsules; this did not interfere with its effect.

### Missed Dose

If a dose of clarithromycin is missed, the patient should take the dose as soon as possible and then return to their normal scheduled dose. However, if a dose is skipped, the patient should not double the next dose.

### Administration

#### **PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)**

PREVACID<sup>®</sup> (lansoprazole delayed-release capsules) should be taken daily before breakfast. Where the product may be used twice daily, it should be taken prior to breakfast and another meal. PREVACID<sup>®</sup> delayed-release capsules **SHOULD NOT BE CRUSHED OR CHEWED**.

### **OVERDOSAGE**

#### **Hp-PAC<sup>®</sup> - Triple Therapy: PREVACID<sup>®</sup>/clarithromycin/amoxicillin**

In case of an overdose, patients should contact a physician, poison control center, or emergency room. There is neither a pharmacologic basis nor any data suggesting an increase in the toxicity of the Hp-PAC<sup>®</sup> combination compared to its individual components.

#### **PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)**

As in all cases where overdosing is suspected, treatment should be supportive and symptomatic. Any unabsorbed material should be removed from the gastrointestinal tract, and the patient should be carefully monitored. 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.

## **BIAXIN<sup>®</sup> BID (clarithromycin tablets, USP, film-coated)**

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. Clarithromycin is protein bound (70%). No data are available on the elimination of clarithromycin by hemodialysis or peritoneal dialysis.

## **AMOXICILLIN (amoxicillin trihydrate) Capsules**

Treatment of overdosage would likely be needed only in patients with severely impaired renal function, since patients with normal kidneys excrete penicillins at a fast rate. Hemodialysis would therefore represent the main form of treatment.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

#### **PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)**

PREVACID<sup>®</sup> (lansoprazole delayed-release capsules) inhibit inhibits the gastric H<sup>+</sup>, K<sup>+</sup>-ATPase (the proton pump) which catalyzes the exchange of H<sup>+</sup> and K<sup>+</sup>. It is effective in the inhibition of both basal acid secretion and stimulated acid secretion.

#### **BIAXIN<sup>®</sup> BID (clarithromycin tablets, USP, film-coated)**

Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible bacteria and suppressing protein synthesis.

### **Pharmacodynamics**

#### **Eradication of *Helicobacter pylori***

*Helicobacter pylori* is considered to be a major factor in the etiology of duodenal ulcer disease. The presence of *H. pylori* may damage the mucosal integrity due to the production of enzymes (catalase, lipases, phospholipases, proteases, and urease), adhesins and toxins; the inflammatory response generated in this manner contributes to mucosal damage.

The concomitant administration of an antimicrobial(s) such as clarithromycin and amoxicillin, and an antisecretory agent such as lansoprazole, improves the eradication of *H. pylori* as compared to individual drug administration. The higher pH resulting from antisecretory treatment, optimizes the environment for the pharmacologic action of the antimicrobial agent(s) against *H. pylori*.

## **PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)**

In healthy subjects, single and multiple doses of lansoprazole delayed-release capsules (15 mg to 60 mg) have been shown to decrease significantly basal gastric acid output and to increase significantly mean gastric pH and percent of time at pH >3 and 4. These doses have also been shown to reduce significantly meal-stimulated gastric acid output and gastric secretion volume. Single or multiple doses of lansoprazole delayed-release capsules (10 mg to 60 mg) reduced pentagastrin-stimulated acid output. In addition, lansoprazole delayed-release capsules have been demonstrated to reduce significantly basal and pentagastrin-stimulated gastric acid secretion among Duodenal Ulcer (DU) and hypersecretory patients, and basal gastric acid secretion among patients with Gastric Ulcer (GU) disease.

A dose-response effect was analyzed by considering the results from clinical pharmacology studies that evaluated more than one dose of lansoprazole delayed-release capsules. The results indicated that, in general, as the dose was increased from 7.5 mg to 30 mg, there was a decrease in mean gastric acid secretion and an increase in the average time spent at higher pH values (pH >4).

The results of pharmacodynamic studies with lansoprazole delayed-release capsules in normal subjects suggest that doses of 7.5 to 10 mg are substantially less effective in inhibiting gastric acid secretion than doses of 15 mg or greater. In view of these results, the doses of lansoprazole delayed-release capsules evaluated in the principal clinical trials ranged from 15 mg to 60 mg daily.

### **Pharmacokinetics**

#### **Hp-PAC<sup>®</sup> - Triple Therapy: PREVACID<sup>®</sup>/clarithromycin/amoxicillin**

The pharmacokinetics of the drugs when all three components of the Hp-PAC<sup>®</sup> (PREVACID<sup>®</sup> capsules, clarithromycin tablets and amoxicillin capsules) were co-administered, has not been studied. Studies have shown no clinically significant interactions between PREVACID<sup>®</sup> and amoxicillin or PREVACID<sup>®</sup> and clarithromycin when co-administered. There is no information about the gastric mucosal concentrations of PREVACID<sup>®</sup>, amoxicillin and clarithromycin after administration of these agents concomitantly. The systemic pharmacokinetic information presented below is based on studies in which each product was administered alone.

#### **PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)**

Lansoprazole delayed-release capsules contain an enteric-coated granule formulation of lansoprazole to ensure that absorption of lansoprazole begins only after the granules leave the stomach (lansoprazole is acid-labile). 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 pharmacokinetics are unaltered by multiple dosing and the drug does not accumulate.

Lansoprazole delayed-release capsules is highly bioavailable when administered orally. In a definitive absolute bioavailability study, the absolute bioavailability was shown to be 86% for a 15 mg capsule and 80% for a 30 mg capsule. First pass effect is apparently minimal.

**Table 6** summarizes the pharmacokinetic parameters ( $T_{max}$ ,  $T_{1/2}$ , AUC and  $C_{max}$ ) of lansoprazole delayed-release capsules in healthy subjects. For a summary of pharmacokinetic, metabolism and excretion data in animals, see **PHARMACOLOGY**).

<b>Table 6</b>				
<b>Pharmacokinetic Parameters of Lansoprazole Delayed-Release Capsules</b>				
<b>Pooled Across Phase 1 Studies</b>				
<b>Parameter</b>	<b><math>T_{max}</math> (h)</b>	<b><math>T_{1/2}</math> (h)</b>	<b>AUC<sup>#</sup> (ng•h/mL)</b>	<b><math>C_{max}</math><sup>#</sup> (ng/mL)</b>
Mean	1.68	1.53	2133	824
Median	1.50	1.24	1644	770
SD	0.80	1.01	1797	419
% CV	47.71	65.92	84.28	50.81
Min	0.50	0.39	213	27
Max	6.00	8.50	14203	2440
N <sup>@</sup>	345	285	513	515

# Normalized to a 30 mg dose  
 @ Number of dosages associated with a parameter

### **BIAXIN<sup>®</sup> BID (clarithromycin tablets, USP, film-coated)**

A summary of clarithromycin pharmacokinetic parameters following the administration of clarithromycin film-coated tablets is provided in **Table 7**. For details see **DETAILED PHARMACOLOGY** in PART II of the Product Monograph.

<b>Table 7</b>				
<b>Clarithromycin Pharmacokinetic Parameters</b>				
<b>Following the Administration of Clarithromycin Film-Coated Tablets</b>				
<b>Single Dose*</b>	<b><math>C_{max}</math> (mg/L)</b>	<b><math>t_{max}</math> (hr)</b>	<b><math>t_{1/2}</math> (hr)</b>	<b>AUC<sub>0-t</sub> (mg•hr/L)</b>
250 mg Mean	1	1.5	2.7	5.47
500 mg Mean	1.77	2.2	--	11.66
Multiple Doses**				
250 mg b.i.d. Mean	1	--	3 to 4	6.34
500 mg b.i.d. Mean	3.38	2.1	5 to 7	44.19

\* Single doses (from Tables 60 & 61)  
 \*\* Multiple doses (from Tables 54 & 61)

## **Absorption:**

### **PREVACID® (lansoprazole delayed-release capsules)**

The absorption of lansoprazole is rapid, with mean peak plasma levels of lansoprazole occurring at approximately 1.7 hours. Peak plasma concentrations of lansoprazole ( $C_{max}$ ) and the area under the plasma concentration curve (AUC) are approximately proportional to dose throughout the range that has been studied (up to 60 mg).

#### Absorption with Food

Food reduces the peak concentration and the extent of absorption by about 50% to 70%. Moreover, the results of a pharmacokinetic study that compared the bioavailability of lansoprazole following a.m. dosing (fasting) versus p.m. dosing (three hours after a meal) indicated that both  $C_{max}$  and AUC values were increased by approximately two-fold or more with a.m. dosing. Therefore, it is recommended that lansoprazole delayed-release capsules be administered in the morning prior to breakfast.

#### Absorption with Antacids

Simultaneous administration of lansoprazole delayed-release capsules with Maalox® (aluminum and magnesium hydroxide) or Riopan® (magaldrate) resulted in lower peak serum levels, but did not significantly reduce the bioavailability of lansoprazole.

In a single-dose crossover study when 30 mg of lansoprazole was administered concomitantly with one gram of sucralfate in healthy volunteers, absorption of lansoprazole was delayed and its bioavailability was reduced. The value of lansoprazole AUC was reduced by 17% and that for  $C_{max}$  was reduced by 21%.

In a similar study when 30 mg of lansoprazole was administered concomitantly with 2 grams of sucralfate, lansoprazole AUC and  $C_{max}$  were reduced by 32% and 55%, respectively. When lansoprazole dosing occurred 30 minutes prior to sucralfate administration,  $C_{max}$  was reduced by only 28% and there was no statistically significant difference in lansoprazole AUC. Therefore, lansoprazole may be given concomitantly with antacids but should be administered at least 30 minutes prior to sucralfate.

### **BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

The absolute bioavailability of 250 mg and 500 mg clarithromycin tablets is approximately 50%. Food slightly delays the onset of clarithromycin absorption but does not affect the extent of bioavailability. Therefore, BIAXIN® BID tablets may be given without regard to meals.

In fasting healthy human subjects, peak serum concentrations are attained within 2 hours after oral dosing. Steady-state peak serum clarithromycin concentrations, which are attained within 2 to 3 days, are approximately 1 mg/L with a 250 mg dose twice daily and 2 to 3 mg/L with a 500 mg dose twice daily. The elimination half-life of clarithromycin is about 3 to 4 hours with 250 mg twice daily dosing but increases to about 5 to 7 hours with 500 mg administered twice daily.

Clarithromycin displays non-linear pharmacokinetics at clinically relevant doses, producing greater than proportional increases in AUC with increasing dose. The degree of non-linearity is reduced on chronic clarithromycin administration (i.e., at steady state). The non-linearity of the pharmacokinetics of the principle metabolite, 14-OH clarithromycin, is slight at the recommended doses of 250 mg and 500 mg administered twice daily. With 250 mg twice daily, 14-OH clarithromycin attains a peak steady state concentration of about 0.6 mg/L and has an elimination half-life of 5 to 6 hours. With a 500 mg twice daily dose, the peak steady-state of 14-OH concentrations of clarithromycin are slightly higher (up to 1 mg/L) and its elimination half-life is about 7 hours. With either dose, the steady-state concentration of this metabolite is generally attained within 2 to 3 days.

*Adult Patients with HIV.* Steady-state concentrations of clarithromycin and 14-OH clarithromycin observed following administration of 500 mg doses of clarithromycin twice a day to adult patients with HIV infection were similar to those observed in healthy volunteers. However, at the higher clarithromycin doses which may be required to treat mycobacterial infections, clarithromycin concentrations can be much higher than those observed at 500 mg clarithromycin doses. In adult HIV-infected patients taking 2000 mg/day in two divided doses, steady-state clarithromycin  $C_{max}$  values ranged from 5 to 10 mg/L.  $C_{max}$  values as high as 27 mg/L have been observed in HIV-infected adult patients taking 4000 mg/day in two divided doses of clarithromycin tablets.

Elimination half-lives appeared to be lengthened at these higher doses as well. The higher clarithromycin concentrations and longer elimination half-lives observed at these doses are consistent with the known non-linearity in clarithromycin pharmacokinetics.

*Clarithromycin and omeprazole.* Clarithromycin 500 mg t.i.d. and omeprazole 40 mg q.d. were studied in fasting healthy adult subjects. When clarithromycin was given alone as 500 mg q8h, the mean steady state  $C_{max}$  value was approximately 3.8 mcg/mL and the mean  $C_{min}$  value was approximately 1.8 mcg/mL. The mean  $AUC_{0-8}$  for clarithromycin was 22.9 mcg·hr/mL. The  $T_{max}$  and half life were 2.1 hrs and 5.3 hrs, respectively, when clarithromycin was dosed at 500 mg t.i.d. When clarithromycin was administered with omeprazole, increases in omeprazole half-life and  $AUC_{0-24}$  were observed. For all subjects combined, the mean omeprazole  $AUC_{0-24}$  was 89% greater and the harmonic mean for omeprazole  $t_{1/2}$  was 34% greater when omeprazole was administered with clarithromycin than when omeprazole was administered alone. When clarithromycin was administered with omeprazole, the steady state  $C_{max}$ ,  $C_{min}$ , and  $AUC_{0-8}$  of clarithromycin were increased by 10%, 27%, and 15%, respectively over values achieved when clarithromycin was administered with placebo.

## AMOXICILLIN (amoxicillin trihydrate) Capsules

Amoxicillin is stable in the presence of gastric acid and is well absorbed from the gastrointestinal tract and may be given with no regard to food. The half-life of amoxicillin is 61.3 minutes.

Orally administered doses of 500 mg amoxicillin capsules result in average peak blood levels 1 to 2 hours after administration in the range of 5.5 to 7.5 mcg/mL.

Detectable serum levels are observed up to eight hours after an orally administered dose of amoxicillin.

### Distribution:

## PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)

The apparent volume of distribution of lansoprazole is approximately 15.7 ( $\pm$  1.9) L, distributing mainly in extracellular fluid. Lansoprazole is 97% bound to plasma proteins. The mean total body clearance (CL) of lansoprazole was calculated at 31  $\pm$  8 L/h, and the volume of distribution ( $V_{ss}$ ) was calculated to be 29 ( $\pm$  4) L.

## BIAXIN<sup>®</sup> BID (clarithromycin tablets, USP, film-coated)

Clarithromycin distributes readily into body tissues and fluids, and provides tissue concentrations that are higher than serum concentrations. Examples from tissue and serum concentrations are presented in **Table 8**.

<b>Table 8</b>		
<b>Representative Clarithromycin Tissue and Serum Concentrations Following the Administration of 250 mg b.i.d of Clarithromycin Film-Coated Tablets</b>		
<b>Tissue Type</b>	<b>Concentrations</b>	
	<b>Tissue (mcg/g)</b>	<b>Serum (mg/L)</b>
Tonsil	1.6	0.8
Lung	8.8	1.7
Leukocytes*	9.2	1.0
* <i>in vitro</i> data.		

## AMOXICILLIN (amoxicillin trihydrate) Capsules

Amoxicillin diffuses readily into most body tissues and fluids, with the exception of brain and spinal fluid, except when the meninges are inflamed. Amoxicillin is not highly protein-bound. In serum, amoxicillin is approximately 20% protein-bound as compared to 60% for penicillin G.

**Metabolism:****PREVACID® (lansoprazole delayed-release capsules)**

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

**BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

Clarithromycin is principally excreted by the liver and kidney. The major metabolite found in urine is 14-OH-clarithromycin.

**Excretion:****PREVACID® (lansoprazole delayed-release capsules)**

Following single dose oral administration of lansoprazole, virtually no unchanged lansoprazole was excreted in the urine. After a 30 mg single oral dose of <sup>14</sup>C-lansoprazole, approximately one-third of the dose was excreted in the urine and approximately two-thirds were recovered in the feces. This implies a significant biliary excretion of the metabolites of lansoprazole.

**BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

At 250 mg twice daily, approximately 20% of an orally administered dose of clarithromycin film-coated tablet is excreted in the urine as the unchanged parent drug. The urinary excretion of unchanged clarithromycin is somewhat greater (approximately 30%) with 500 mg twice daily dosing. The renal clearance of clarithromycin is, however, relatively independent of the dose size and approximates the normal glomerular filtration rate. The major metabolite found in urine is 14-OH-clarithromycin which accounts for an additional 10 to 15% of the dose with twice daily dosing at either 250 mg or 500 mg. Most of the remainder of the dose is eliminated in the feces, primarily via the bile. About 5 to 10% of the parent drug is recovered from the feces. Fecal metabolites are largely products of N-demethylation, 14-hydroxylation or both.

**AMOXICILLIN (amoxicillin trihydrate) Capsules**

Most of the amoxicillin is excreted unchanged in urine; its excretion can be delayed by concurrent administration of probenecid.

Approximately 60% of an orally administered dose of amoxicillin is excreted in the urine within 6 to 8 hours.

### **Special Populations and Conditions**

#### **Pediatrics:**

##### **Hp-PAC<sup>®</sup> - Triple Therapy: PREVACID<sup>®</sup>/clarithromycin/amoxicillin**

The safety and effectiveness of Hp-PAC<sup>®</sup> in pediatric patients infected with *H. pylori* have not been established.

#### **Geriatrics:**

##### **PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)**

The results from the studies that evaluated the pharmacokinetics of lansoprazole following oral administration in an older population revealed that in comparison with younger subjects, older subjects exhibited significantly larger AUCs and longer  $t_{1/2}$ s. Lansoprazole did not accumulate in the older subjects upon multiple dosing since the longest mean  $t_{1/2}$  in the studies was 2.9 hours, and lansoprazole is dosed once daily.  $C_{max}$  in the elderly was comparable to that found in adult subjects.

##### **BIAXIN<sup>®</sup> BID (clarithromycin tablets, USP, film-coated)**

In a steady-state study in which healthy elderly subjects (age 65 to 81 years old) were given 500 mg of clarithromycin every 12 hours, the maximum concentrations of clarithromycin and 14-OH clarithromycin were increased. The AUC was also increased. These changes in pharmacokinetics parallel known age-related decreases in renal function. In clinical trials, elderly patients did not have an increased incidence of adverse events when compared to younger patients. (See **WARNINGS AND PRECAUTIONS – Renal**)

#### **Gender:**

In a study comparing 12 male and six female subjects, no gender differences were found in pharmacokinetics or intragastric pH results (see **PRECAUTIONS; Use in Women**).

#### **Race:**

The pooled pharmacokinetic parameters of oral administered lansoprazole from twelve U.S. Phase I studies (N=513) were compared to the mean pharmacokinetic parameters from two Asian studies (N=20). The mean AUCs of lansoprazole in Asian subjects are approximately twice that seen in pooled U.S. data, however, the inter-individual variability is high. The  $C_{max}$  values are comparable.

## **Hepatic Insufficiency:**

### **PREVACID® (lansoprazole delayed-release capsules)**

As would be expected with a drug that is primarily metabolized by the liver, in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) chronic hepatic disease, the plasma half-life of the drug after oral administration increased to 5.2 hours compared to the 1.5 hours half-life in healthy subjects. An increase in AUC of 3.4 fold was observed in patients with hepatic impairment versus healthy subjects (7096 versus 2645 ng•h/mL) which was due to slower elimination of lansoprazole; however,  $C_{max}$  was not significantly affected. Dose reduction in patients with severe hepatic disease should be considered.

### **BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

The steady-state concentrations of clarithromycin in subjects with impaired hepatic function did not differ from those in normal subjects; however, the 14-OH clarithromycin concentrations were lower in the hepatically impaired subjects. The decreased formation of 14-OH clarithromycin was at least partially offset by an increase in renal clearance of clarithromycin in subjects with impaired hepatic function when compared to healthy subjects (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

## **Renal Insufficiency:**

### **PREVACID® (lansoprazole delayed-release capsules)**

In patients with mild ( $Cl_{cr}$  40 to 80 mL/min), moderate ( $Cl_{cr}$  20 to 40 mL/min) and severe ( $Cl_{cr}$  <20 mL/min) chronic renal impairment, the disposition of lansoprazole after oral administration was very similar to that of healthy volunteers.

The impact of dialysis on lansoprazole was evaluated from a pharmacokinetic standpoint, and there were no significant differences in AUC,  $C_{max}$  or  $t_{1/2}$  between dialysis day and dialysis-free day. Dialysate contained no measurable lansoprazole or metabolite. Lansoprazole is not significantly dialysed.

### **BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

The pharmacokinetics of clarithromycin was also altered in subjects with impaired renal function. The elimination of clarithromycin was impaired in patients with impaired renal function (see **WARNINGS AND PRECAUTIONS** – **Renal** and **DOSAGE AND ADMINISTRATION**).

## STORAGE AND STABILITY

Store the Hp-PAC<sup>®</sup> blister cards between 15 and 25°C. Protect from light and moisture.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

### Composition

#### **Hp-PAC<sup>®</sup> - *H. pylori* Individual Daily Administration Blister Pack**

Each triple therapy Hp-PAC<sup>®</sup> (lansoprazole/clarithromycin/amoxicillin) daily administration blister pack contains:

#### **PREVACID<sup>®</sup> (lansoprazole delayed-release capsules):**

- two opaque, hard gelatin, pink and black lansoprazole 30 mg capsules, with the TAP logo and "PREVACID 30" imprinted on the capsules.

Medicinal Ingredient: Each delayed-release capsules contains 30 mg of lansoprazole in the form of enteric-coated granules for oral administration.

Non-Medicinal Ingredients: Each PREVACID<sup>®</sup> delayed-release capsule also contains the following non-medicinal ingredients:—cellulosic polymers, colloidal silicon dioxide, D&C Red No. 28, FD&C Blue No. 1, FD&C Red No. 40, gelatin, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar spheres, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide.

#### **BIAXIN<sup>®</sup> BID (clarithromycin tablets, USP, film-coated):**

- two pale yellow, oval, film-coated clarithromycin 500 mg tablets, with the Abbott logo printed on one side.

Medicinal Ingredient: Each oval, printed with Abbott logo on one side, pale yellow film-coated BIAXIN<sup>®</sup> BID tablet contains 500 mg of clarithromycin for oral administration.

Non-Medicinal Ingredients: Each BIAXIN<sup>®</sup> BID 500 mg tablet also contains the following non-medicinal ingredients: cellulosic polymers, croscarmellose sodium, D&C Yellow No.10, magnesium stearate, povidone, propylene glycol, silicon dioxide, sorbic acid, sorbitan monooleate, stearic acid, talc, titanium dioxide and vanillin. BIAXIN<sup>®</sup> BID does not contain tartrazine.

### **AMOXICILLIN (amoxicillin trihydrate) Capsules:**

- four opaque, scarlet and yellow amoxicillin capsules, with the Abbott logo and “500” imprinted on the capsules.

Medicinal Ingredient: Each amoxicillin capsule contains 500 mg of amoxicillin trihydrate.

Non-Medicinal Ingredients: Each Amoxicillin 500 mg capsule also contains the following non-medicinal ingredients: colloidal silicon dioxide, D&C Yellow No. 10, dry-flo starch, FD&C Blue No. 1, FD&C Red No. 3, FD&C Red No. 40, FD&C Yellow No. 6, gelatin, magnesium stearate, sodium lauryl sulfate, talc and titanium dioxide. Gluten- and tartrazine-free.

Hp-PAC<sup>®</sup> daily administration blister packs are available in boxes containing seven (7) days of therapy.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

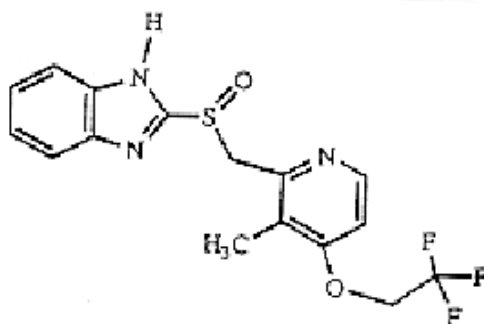
#### PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)

Proper name: Lansoprazole

Chemical name: 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-benzimidazole

Molecular formula  
and molecular mass: C<sub>16</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>S and 369.37

Structural formula:



Physicochemical properties:

Lansoprazole is a white to brownish-white odourless, crystalline powder which melts with decomposition at approximately 166°C. Lansoprazole is freely soluble in dimethylformamide; slightly soluble in methanol; sparingly soluble in ethanol; slightly soluble in ethyl acetate, dichloromethane and acetonitrile; very slightly soluble in ether; and practically insoluble in water and hexane.

The rate of degradation of the compound in aqueous solution increases with decreasing pH. It has an octanol/water partition coefficient of 240 at pH 7.

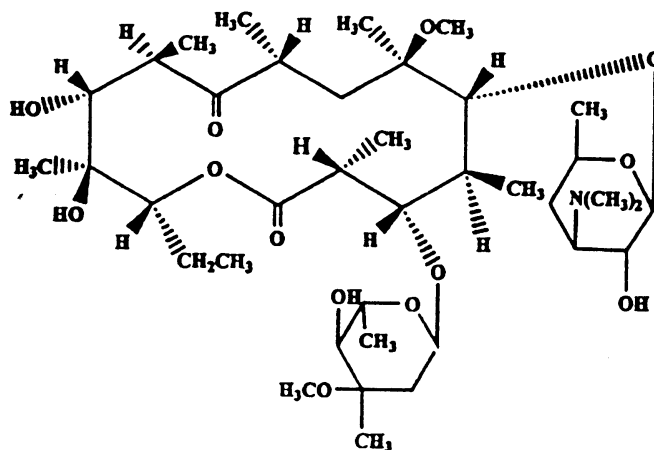
## BIAXIN<sup>®</sup> BID (clarithromycin tablets, USP, film-coated)

Proper name: Clarithromycin

Chemical name: (3R\*, 4S\*, 5S\*, 6R\*, 7R\*, 9R\*, 11R\*, 12R\*, 13S\*, 14R\*)-4-[(2,6-dideoxy-3-C-methyl-3-O-methyl- $\alpha$ -L-ribo-hexopyranosyl)oxy]-14-ethyl-12,13-dihydroxy-7-methoxy-3,5,7,9,11,13-hexamethyl-6-[[[3,4,6-trideoxy-3-(dimethylamino)- $\beta$ -D-xylo-hexopyranosyl]oxy]oxacyclotetradecane-2-10-dione.

Molecular formula  
and molecular mass: C<sub>38</sub>H<sub>69</sub>NO<sub>13</sub> and 747.96

Structural formula:



Physicochemical properties: Clarithromycin is a white to off-white crystalline powder. It is slightly soluble in methanol, ethanol and acetonitrile, and practically insoluble in water. The pK<sub>a</sub> of clarithromycin is 8.48; the pH of a 0.2% (Methanol:Water, 5:95) slurry is 8.8.

The partition coefficient of clarithromycin is influenced by the pH of the water phase and polarity of the organic phase. For octanol (dipole moment = 0.25): water, the partition co-efficient varies from 5.63 to 46.0 for pH water increases from 2 to 8. The melting point of clarithromycin is approximately 225 °C.

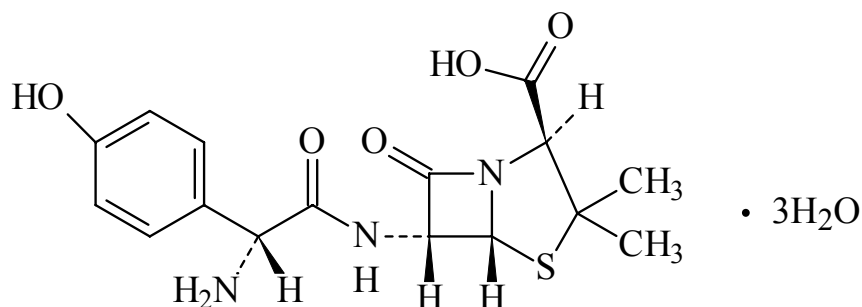
## AMOXICILLIN (amoxicillin trihydrate capsules)

Proper name: amoxicillin trihydrate

Chemical name: trihydrate of 6-[D-(-)-alpha-amino-4-hydroxyphenyl-acetamido]-penicillanic acid.

Molecular formula and molecular mass:  $C_{16}H_{19}N_3O_5 \cdot 3H_2O$  and 419.5

Structural formula:



Physicochemical properties: Amoxicillin trihydrate is a white practically odourless crystalline powder, slightly soluble in water and in methanol; insoluble in benzenes, in chloroform and in ether.

## CLINICAL TRIALS

### ***Helicobacter pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence**

Randomized, double-blind clinical studies in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer in the last year) evaluated the efficacy of lansoprazole delayed-release capsules in combination with amoxicillin capsules and clarithromycin tablets as triple 14-day therapy, or lansoprazole delayed-release capsules in combination with amoxicillin as dual 14-day therapy for the eradication of *H. pylori*. Based on the results of these studies, the safety and efficacy of two different eradication regimens were established:

Triple therapy: PREVACID® 30 mg b.i.d./clarithromycin 500 mg b.i.d./amoxicillin 1 g b.i.d.

All treatments were for 14 days. *H. pylori* eradication was defined as two negative tests (culture and histology) at 4 to 6 weeks following the end of treatment.

Triple therapy was shown to be more effective than all possible dual therapy combinations (**Table 9**). Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

A randomized, double-blind clinical study performed in the U.S. in patients with *H. pylori* and duodenal ulcer disease (defined as an active ulcer or history of an ulcer within one year) compared the efficacy of lansoprazole delayed-release capsules triple therapy for 10 and 14 days. This study established that the 10-day triple therapy was equivalent to the 14-day triple therapy in eradicating *H. pylori* (**Table 9**).

<b>Table 9</b> <b><i>H. pylori</i> Eradication Rates – Triple Therapy (PREVACID®/clarithromycin/amoxicillin)</b> <b>Percent of Patients Cured [95% Confidence Interval] (Number of Patients)</b>			
<i>Study Number</i>	<b>Duration</b>	<b>Triple Therapy Evaluable Analysis*</b>	<b>Triple Therapy Intent-to-Treat Analysis<sup>#</sup></b>
Trial #1 (M93-131)	14 days	92 <sup>†</sup> [80.0 – 97.7] (N=48)	86 <sup>†</sup> [73.3 – 93.5] (N=55)
Trial #2 (M95-392)	14 days	86 <sup>§</sup> [75.7 – 93.6] (N=66)	83 <sup>§</sup> [72.0 – 90.8] (N=70)
Trial #3 (M95-399) <sup>+</sup>	14 days	85 [77.0 – 91.0] (N=113)	82 [73.9 – 88.1] (N=126)
	10 days	84 [76.0 – 89.8] (N=123)	81 [73.9 – 87.6] (N=135)

\* Based on evaluable patients with confirmed duodenal ulcer (active or within one year) and *H. pylori* infection at baseline defined as at least two of three positive endoscopic tests from CLOtest® (Delta West Ltd., Bentley, Australia), histology and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy.

<sup>#</sup> Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and had a confirmed duodenal ulcer (active or within one year). All dropouts were included as failures of therapy.

<sup>†</sup> (p<0.05) versus PREVACID®/amoxicillin and PREVACID®/clarithromycin dual therapy.

<sup>§</sup> (p<0.05) versus clarithromycin/amoxicillin dual therapy.

<sup>+</sup> The 95% confidence interval for the difference in eradication rates, 10-day minus 14-days is (-10.5, 8.1) in the evaluable analysis and (-9.7, 9.1) in the intent-to-treat analysis.

A randomized, open-label, parallel-group, multicenter clinical study performed in the U.K. in patients with *H. pylori* and duodenal ulcer disease and/or gastritis, compared the efficacy and safety of four 7-day triple therapy treatment regimens. The primary efficacy measure was eradication of *H. pylori* as defined by a negative <sup>13</sup>C-urea breath test at least 28 days (Visit 3) after completing study medication. This study established that 7-day triple therapy with PREVACID<sup>®</sup>/clarithromycin/amoxicillin was as clinically effective in eradication *H. pylori* as the 10 or 14-day treatment regimens (**Table 10**).

<b>Table 10</b>	
<b>Posttreatment Breath Test Results by Patient Population</b>	
<b><i>H. pylori</i> Eradication Rates – Triple Therapy Regimen (PREVACID<sup>®</sup>/clarithromycin/amoxicillin)</b>	
<b>Population</b>	<b>Treatment Group</b>
<b>Trial # 4 (GB 94/110)</b>	<b>LAC</b>
<i>Evaluable (Per Protocol)</i> *	
Positive n (%)	11 (9.6)
Negative n (%)	103 (90.4)
95% CI (eradication rate)	83.0, 94.8
<i>Intent-to-Treat</i> <sup>#</sup>	
Positive n (%)	12 (10.3)
Negative n (%)	104 (89.7)
95% CI (eradication rate)	82.3, 94.3
<i>Intent-to-Treat</i> (Worst Case)**	
Positive n (%)	17 (14.0)
Negative n (%)	104 (86.0)
95% CI (eradication rate)	78.2, 91.4
<i>Intent-to-Treat</i> (Best Case)**	
Positive n (%)	12 (9.9)
Negative n (%)	109 (90.1)
95% CI (eradication rate)	83.0, 94.5
<p>* Based on evaluable patients with confirmed duodenal ulcer and/or gastritis and <i>H. pylori</i> infection at baseline defined as at least two of three positive endoscopic tests from CLOtest<sup>®</sup>, histology and/or culture. Patients were included in the analysis if they completed the study. Additionally, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the analysis as failures of therapy.</p> <p>** “Worst case” assumed that missing Visit 3 breath test results were positive for <i>H. pylori</i> and “Best case” results assumed that missing Visit 3 results were negative for <i>H. pylori</i>.</p> <p># Patients were included in the analysis if they had documented <i>H. pylori</i> infection at baseline as defined above and had a confirmed duodenal ulcer.</p> <p>LAC lansoprazole 30 mg b.i.d. + amoxicillin 1 g b.i.d. + clarithromycin 250 mg b.i.d.</p>	

A combination of PREVACID<sup>®</sup> plus clarithromycin and amoxicillin as triple therapy, was effective in eradicating *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

There were no statistically significant differences in *H. pylori* eradication rates between the levels of any potentially influential factors, including baseline duodenal ulcer status, baseline duodenal ulcer size, gender, age, race, or tobacco use for the evaluable, intent-to-treat (all available data), and modified intent-to-treat (worst case) analyses. *H. pylori* eradication rates at the Week 6 Visit for patients who received lansoprazole 30 mg b.i.d., clarithromycin 500 mg b.i.d., and amoxicillin 1 g b.i.d. are presented by concomitant factors in **Tables 11** and **12** for the 14-day and 10-day treatment studies, respectively.

A statistically significant difference in ulcer prevalence rates was observed between the levels for age in the evaluable, intent-to-treat (all available data), and modified intent-to-treat (worst case) analyses, with younger patients demonstrating a lower ulcer prevalence rate compared with older patients. No statistically significant differences in ulcer prevalence rates were observed between the levels of other potentially influential factors including baseline duodenal ulcer status, baseline duodenal ulcer size, gender, race, or tobacco use for the evaluable, intent-to-treat (all available data), and modified intent-to-treat (worst case) analyses.

A statistically significant difference in *H. pylori* eradication rates was observed between the levels of baseline duodenal ulcer size in the evaluable and intent-to-treat (all available data) analyses, with patients who had smaller ulcers (3 to 5 mm) demonstrating a lower *H. pylori* eradication rate compared with patients who had larger ulcers. Statistically significant differences in *H. pylori* eradication rates were also observed between the levels of age in the intent-to-treat (all available data) and modified intent-to-treat (worst case) analyses, with patients over 65 years of age demonstrating a higher *H. pylori* eradication rate compared with patients less than or equal to 65 years of age. No statistically significant differences in *H. pylori* eradication rates were observed between the levels of other potentially influential factors including baseline duodenal ulcer status, gender, race, or tobacco use for the evaluable, intent-to-treat (all available data), and modified intent-to-treat (worst case) analyses.

<b>Table 11</b>			
<b><i>H. pylori</i> Eradication Rates at the Week 6 Visit for Patients Who Received 14 days of Lansoprazole 30 mg b.i.d., Clarithromycin 500 mg b.i.d., and Amoxicillin 1 g b.i.d.</b>			
<b>By Concomitant Factors</b>			
<b>Factor</b>	<b>% (n/N)</b>		
	<b>Evaluable</b>	<b>Intent-to-Treat (All Available Data)</b>	<b>Modified Intent-to-Treat (Worst Case)</b>
<i>Baseline DU Status</i>			
Active	88% (88/100)	89% (91/102)	83% (91/110)
Historical	93% (13/14)	93% (14/15)	93% (14/15)
<i>Baseline DU Size</i>			
3 – 5 mm	85% (23/27)	86% (24/28)	83% (24/29)
>5 – 10 mm	89% (55/62)	92% (57/62)	84% (57/68)
>10 mm	91% (10/11)	83% (10/12)	77% (10/13)
<i>Gender</i>			
Female	89% (31/35)	89% (32/36)	84% (32/38)
Male	89% (70/79)	90% (73/81)	84% (73/87)
<i>Age</i>			
<45	87% (46/53)	88% (50/57)	83% (50/60)
45-65	92% (43/47)	92% (43/47)	84% (43/51)
>65	86% (12/14)	92% (12/13)	86% (12/14)
<i>Race</i>			
Black	82% (22/27)	82% (23/28)	79% (23/29)
Caucasian	92% (57/62)	91% (59/65)	83% (59/71)
Other	88% (22/25)	96% (23/24)	92% (23/25)
<i>Tobacco Use</i>			
Nonusers <sup>§</sup>	89% (56/63)	92% (58/63)	87% (58/67)
User	88% (45/51)	87% (47/54)	81% (47/58)
No statistically significant differences were observed between the levels of any factor after stratification by study			
§ Includes ex-tobacco users			

<b>Table 12</b>			
<b><i>H. pylori</i> Eradication Rates at the Week 6 Visit for Patients Who Received 10 days of Triple Therapy (Lansoprazole 30 mg b.i.d., Clarithromycin 500 mg b.i.d., and Amoxicillin 1 g b.i.d.) by Concomitant Factors</b>			
<b>Factor</b>	<b>% (n/N)</b>		
	<b>Evaluable</b>	<b>Intent-to-Treat (All Available Data)</b>	<b>Modified Intent-to-Treat (Worst Case)</b>
<i>Baseline DU Status</i>			
Active	86% (91/106)	88% (97/110)	83% (97/117)
Historical	71% (12/17)	72% (13/18)	72% (13/18)
<i>Baseline DU Size<sup>#</sup></i>			
3 – 5 mm	77% (34/44)	80% (36/45)	75% (36/48)
>5 – 10 mm	91% (43/47)	94% (47/50)	90% (47/52)
>10 mm	92% (14/15)	93% (14/15)	82% (14/17)
<i>Gender</i>			
Female	79% (38/48)	82% (42/51)	79% (42/53)
Male	87% (65/75)	88% (68/77)	83% (68/82)
<i>Age</i>			
<45	85% (33/39)	85% (35/41)	80% (35/44)
45-65	82% (56/68)	86% (61/71)	81% (61/75)
>65	88% (14/16)	88% (14/16)	88% (14/16)
<i>Race</i>			
Black	84% (16/19)	90% (18/20)	78% (18/23)
Caucasian	82% (62/76)	83% (66/80)	80% (66/82)
Other	89% (25/28)	93% (26/28)	87% (26/30)
<i>Tobacco Use</i>			
Nonusers <sup>§</sup>	83% (59/71)	87% (65/75)	81% (65/80)
User	85% (44/52)	85% (45/53)	82% (45/55)
No statistically significant differences were observed among the levels of any factor			
# Includes only patients with active DU at baseline			
§ Includes ex-tobacco users			

A statistically significant difference in ulcer prevalence rates was observed between baseline DU status (active or historical) in the evaluable, intent-to-treat (all available data), and modified intent-to-treat (worst case) analyses, with patients who had a historical duodenal ulcer at baseline demonstrating a lower ulcer prevalence rate compared with patients who had an active duodenal ulcer at baseline. No statistically significant differences in ulcer prevalence rates were observed among the levels of other potentially influential factors including baseline duodenal ulcer size, gender, age, race, or tobacco use for the evaluable, intent-to-treat (all available data), and modified intent-to-treat (worst case) analyses.

## DETAILED PHARMACOLOGY

### In Animals

#### PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)

##### Pharmacodynamics

Studies of the preclinical pharmacology of lansoprazole have delineated its mechanism of action with *in vitro* investigations and have demonstrated *in vivo* efficacy. The orally administered compound appears to gain access to gastric parietal cells as the uncharged parent with conversion in the secretory canaliculus to charged metabolites that bind directly to a sulfhydryl group on the canalicular (H<sup>+</sup>,K<sup>+</sup>)-ATPase. *In vivo* comparisons with the histamine H<sub>2</sub>-receptor antagonist (H<sub>2</sub>-RA) famotidine have revealed that in preventing ulcer induction or in accelerating healing, famotidine shows greater potency but is not as universal in its effect as lansoprazole. Famotidine fails to suppress acid secretion induced by stress and deoxyglucose and also fails to prevent gastric lesions induced by ethanol. Further, famotidine is significantly less potent than lansoprazole in preventing esophagitis resulting from reflux and decreased mucosal resistance. Chronically, famotidine is significantly less potent than lansoprazole in healing gastric ulcers (GUs) and duodenal ulcers (DUs).

These data suggest that lansoprazole has a potency profile comparable to that of another proton-pump inhibitor, omeprazole; while potency with respect to H<sub>2</sub>-RAs may not be as great, more comprehensive suppression of acid secretion is achieved with associated acceleration of lesion healing.

General pharmacology investigations have not revealed identifiable tendencies in animal models for lansoprazole to induce untoward side effects. No contraindicated effects could be detected in the gastrointestinal (GI) system. Smooth muscle contraction and GI transit are unaffected by lansoprazole at doses 200 times greater than those anticipated in humans. Beneficial effects of the compound have been observed on gastric hemodynamics in experimental shock. No notable neuropharmacologic results have been observed. No effects of lansoprazole have been observed on muscle relaxation, anticonvulsant activity, analgesia, or hypothermic responses. Both central and autonomic responses are also free of detectable effects of the compound.

Results on cardiovascular pharmacology are, similarly, without physiologic significance. No notable effects were observed on blood pressure, heart rate, or respiration at doses in excess of 600-fold greater than the anticipated dose in humans. Similarly, water and electrolyte balance are unperturbed by lansoprazole.

The combination of both *in vitro* and *in vivo* efficacy for this inhibitor of the gastric proton pump has been demonstrated to be comparable to another member of its class, omeprazole. Its efficacy profile has been found superior to a representative H<sub>2</sub>-RA, famotidine. Notable absence of untoward side effects has been demonstrated over a wide range of animal species and suggests a highly specific site of action in the acid secretory compartment of the gastric parietal cell.

## Pharmacokinetics

After oral doses of  $^{14}\text{C}$ -lansoprazole in gum arabic suspensions or in gelatin capsules, 27% of the radioactivity was absorbed in mice, 37% in rats, and 63 to 87% in dogs. However, due to degradation and hepatic metabolism of the absorbed dose, bioavailability was much lower, representing 4% in mice and rats and 22% in dogs. Peak levels of parent drug in mice, rats, and dogs were reached within two hours after dosing, and plasma concentrations generally increased with dose size. Considerable interanimal variability was found in monkeys, and  $C_{\text{max}}$  values occurred from 0.5 to six hours after a 50 mg/kg oral dose in gum arabic. Following an oral dose of lansoprazole, AUC values ranged from 10 to 1230 ng•h/mL in mice (1.5 to 50 mg/kg), 30 to 9639 ng•h/mL in rats (2 to 150 mg/kg), 450 to 8800 ng•h/mL in dogs (0.5 to 50 mg/kg), and  $4750 \pm 4990$  ng•h/mL in monkeys (50 mg/kg). The half-life of lansoprazole ranged from 0.2 to 1.2 hours in mice and rats and had a tendency to increase with dose size; the half-life in dogs averaged 0.6 to 1.7 hours, and in monkeys was 3.3 hours. The AUC and  $C_{\text{max}}$  parameters were reasonably consistent after multiple doses of lansoprazole in mice and rats, were variable in monkeys, and decreased appreciably in dogs. The pharmacokinetic data for lansoprazole is summarized in **Table 13**. (For pharmacokinetic parameters of lansoprazole in humans, see **ACTION AND CLINICAL PHARMACOLOGY**.) Following oral or IV administration of a 2 mg/kg dose of racemic lansoprazole to rats and dogs,  $C_{\text{max}}$  and/or AUC values were about two to threefold greater for the (+) enantiomer than the (-) enantiomer. *In vitro* studies with racemic lansoprazole and the individual isomers using rat and dog liver 9000 x g supernatants suggested that the (-) isomer is metabolized more rapidly than the (+) isomer, resulting in lower plasma concentrations of the (-) isomer. Both enantiomers apparently inhibit acid secretion to about the same extent.

Circulating metabolites in rats and dogs included the sulfide (M-I), benzimidazole (M-III), the 5-hydroxysulfide (M-IV), 5-hydroxylansoprazole (M-VI), the sulfone (M-VII), the 5-hydroxysulfone (M-IX) and the hydroxymethyl metabolite (M-X), (see Figure 1). Pharmacokinetic characterization of these metabolites has not been done. However, studies of total uncharacterized metabolites have demonstrated that, based on  $C_{\text{max}}$  values after oral doses, the plasma levels exceed those of parent drug by 1.3 to 19 fold in mice, rats, and dogs. The half-life of the metabolites averaged one to three hours in mice, and eight to 11 hours in rats and dogs.

<b>Table 13</b>			
<b>Summary of Pharmacokinetic, Metabolism and Excretion Data</b>			
<b>For Lansoprazole in Animals</b>			
<b>Parameter</b>	<b>Mouse</b>	<b>Rat</b>	<b>Dog</b>
<i>Oral Doses (mg/kg)</i>	<i>(1.5-50)</i>	<i>(2-150)</i>	<i>(0.5-50)</i>
<b>Plasma</b>			
<i>Lansoprazole</i>			
C <sub>max</sub> (ng/mL)	30 - 1840	10 - 2872	350 - 3470
T <sub>max</sub> (h)	0.17 - 0.34	0.25 - 2	0.25 - 2
T <sub>1/2</sub> (h)	0.2 - 1.1	0.3 - 1.2	0.6 - 1.7
AUC (ng•h/mL)	10 - 1230	30 - 9639	450 - 8800
<i>Metabolites</i>			
C <sub>max</sub> (ng Eq/mL)	210 - 15600	140 - 4290	450 - 7490
T <sub>max</sub> (h)	0.17 - 0.34	0.5 - 1	1 - 2
T <sub>1/2</sub> (h)	1.4 - 3.1	8 - 11.9	7.9 - 11.1
AUC (ng Eq•h/mL)	260 - 17370	1130 - 38100	4410 - 62700
<b>Excretion</b>			
Urine (% Dose)		17.9	12 - 24.6
Feces (% Dose)		81.0	67.5 - 83.7
Bile (% Dose)		59.6	42.6
<b>Metabolism</b>			
<i>Urine (% Dose)</i>			
Lansoprazole		0.1	0 - 0.1
M-II to M-V		1.4 - 1.9	0.2 - 1.5
M-VI to M-IX		0.2 - 1.3	0.2 - 1.3
M-X		3.6	1.3
<i>Feces (% Dose)</i>			
Lansoprazole		0.8	0 - 1.2
M-I, M-III		0.7 - 1.0	0.7 - 1.5
M-II		8.7	0 - 14.8
M-IV		18.5	14.9 - 33.4
M-V to M-X		0.6 - 1.7	0.7 - 3.5
<i>Bile (% Dose)</i>			
Lansoprazole		0.2	
M-I to M-III		0.1 - 1.5	
M-IV		10.7	6.0
M-V, M-VII, M-VIII		0.6 - 1.0	
M-VI		1.8	8.0
M-IX		4.1	3.7
Metabolites M-I through M-X are identified in Figure 1			

### Protein Binding

Lansoprazole was extensively bound to plasma proteins. At lansoprazole concentrations ranging from 10 to 5000 ng/mL, protein binding ranged from 92 to 96% in rat and dog plasma. Binding of the drug to mouse plasma proteins has not been studied.

## Distribution and Accumulation

The distribution and accumulation of lansoprazole in tissues have been studied in rats, and one accumulation study was done in mice. No tissue distribution studies have been reported in dogs. Lansoprazole was rapidly distributed throughout the body of rats after a 2 mg/kg oral dose, with relatively high concentrations in the intestine, stomach, liver, kidney, and thyroid. Tissue to plasma ratios of two to 35 were noted in these tissues. Concentrations in the brain and all other tissues examined were lower than circulating levels. After multiple oral doses (2 mg/kg/day) for seven days, radioactivity in plasma and tissues was slightly elevated, and the overall distribution patterns were similar. The cumulative excretion curves paralleled the administered dose, suggesting little accumulation of the drug in tissues with daily dosing. In both the single- and multiple-dose studies, most of the drug was cleared from all tissues except the thyroid after 72 hours. The tissue distribution pattern in mice 24 hours after a single, oral 1.5 mg/kg dose was comparable to that seen in rats. Accumulation of the dose in plasma and practically all tissues of mice and rats was observed after large oral doses of 50 mg/kg/day for 26 days.

Lansoprazole readily penetrated into the parietal cells of the gastric mucosa of rats and persisted for 24 hours. Levels of parent drug in the mucosa were two to fivefold greater than those in plasma up to six hours after a 2 mg/kg iv dose, supporting the concept that lansoprazole suppresses acid secretion by inhibiting the (H<sup>+</sup>,K<sup>+</sup>)-ATPase enzyme located in these cells.

## Enzyme Induction and Inhibition

Daily, oral administration of a 150 mg/kg dose of lansoprazole to rats for five days resulted in a moderate induction of microsomal, mixed function oxidase enzymes in the liver. Microsomal protein, total cytochrome P-450, and cytochrome b<sub>5</sub> levels were increased 12 to 45%, while activities of p-nitroanisole O-demethylase and p-nitrophenyl glucuronyltransferase were elevated about two to threefold. Moreover, incubation of lansoprazole with rat liver microsomes (60 to 1500 mcg/g liver) inhibited the *in vitro* metabolism of aminopyrine, aniline, and p-nitroanisole from 8 to 71%. The data suggested that acute doses may inhibit some drug-metabolizing enzymes, while chronic doses induce their formation.

## Metabolic Pathways

*In vitro* studies demonstrated that lansoprazole was preferentially metabolized by the liver in rats, but metabolic activity was also found in whole blood, kidney, and especially rat fecal contents. The drug is acid labile, and intestinal degradation has also been reported. A total of ten metabolites (designated as M-I to M-X) have been identified in biologic samples from rats and dogs. Many of the metabolites were found as sulfate or glucuronic acid conjugates. The metabolic scheme is illustrated in Figure 1.

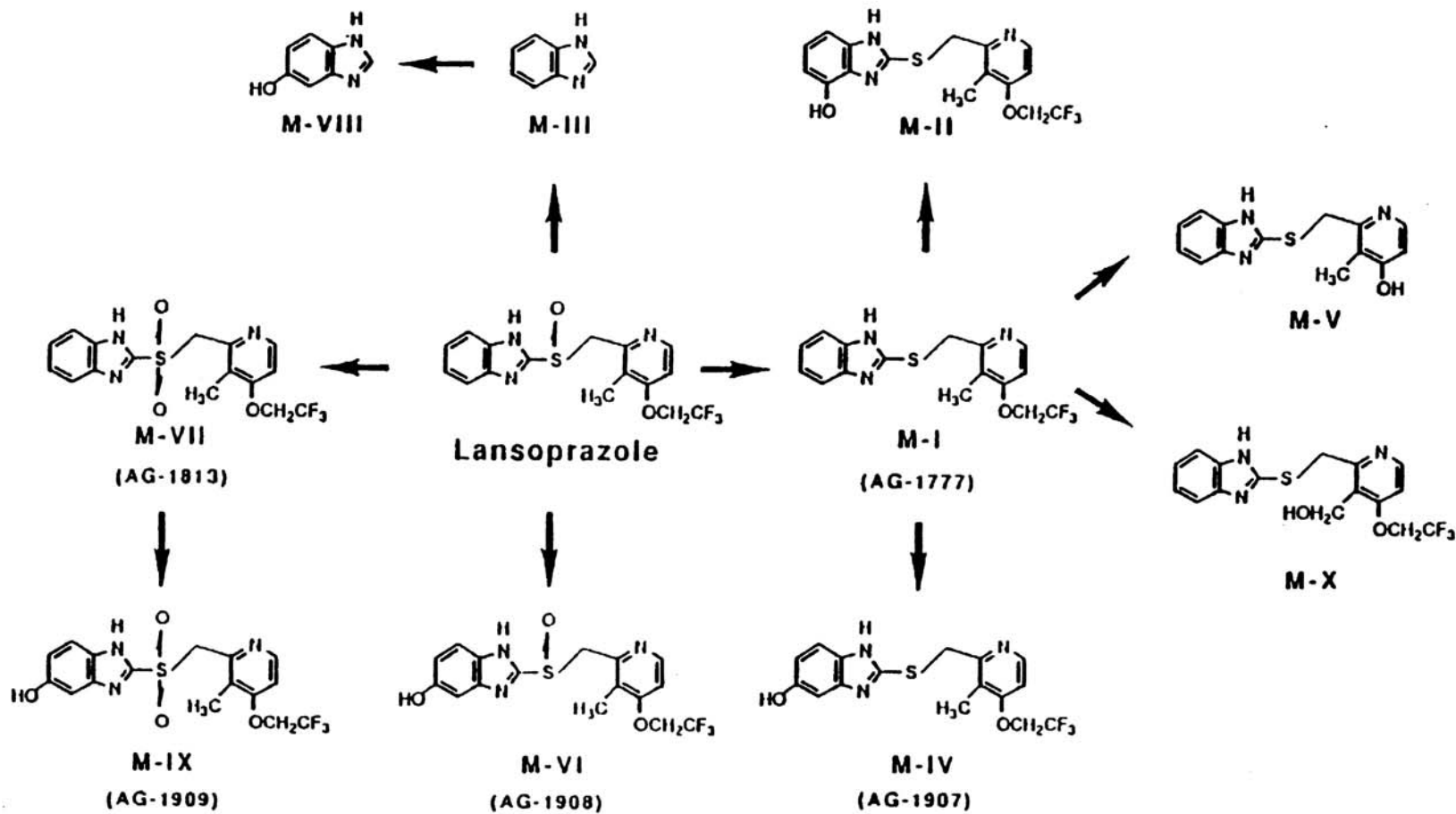


Figure 1: Postulated Metabolic Pathway of Lansoprazole in Rats and Dogs

Lansoprazole is metabolized by the following pathways: 1) reduction and oxidation of the sulfoxide group to form the sulfide (M-I) and sulfone (M-VII); 2) hydroxylation on the benzimidazole ring to give 6-hydroxysulfide (M-II), 5-hydroxysulfide (M-IV), 5-hydroxylansoprazole (M-VI), 5-hydroxybenzimidazole (M-VIII), and 5-hydroxysulfone (M-IX); 3) hydroxylation of the methyl group on the pyridine ring (M-X); 4) dealkylation (M-V); and 5) elimination of the pyridylmethylsulfanyl group to form benzimidazole (M-III).

### Excretion

Both urinary and fecal excretion were involved in eliminating lansoprazole and its metabolites from the body. About 12 to 25% of the dose was found in the urine, while 68 to 84% was excreted into the feces, primarily via the bile. Metabolites M-II through M-X (free and conjugated) were found in the urine of rats and dogs and represented 0.2 to 3.6% of the dose. The sulfide (M-I) and free parent drug were not detected in urine.

Unchanged lansoprazole was a minor fecal component (approximately 1% of the dose), while the major metabolites were identified as the free 5-hydroxysulfide (M-IV) and the 4-hydroxysulfide (M-II), representing about 15 to 33 and 9 to 15% of the dose in rats and dogs, respectively. The remaining eight metabolites were also detected, and each accounted for 0.6 to 3.5% of the dose, but about half of the metabolites were not characterized. Metabolite profiles in rat bile showed that, except for the hydroxymethyl metabolite (M-X), all other identified metabolites were present. The 5-hydroxysulfide (M-IV), 5-hydroxylansoprazole (M-VI) and the 5-hydroxysulfone (M-IX) were major components of rat and dog bile, representing 6 to 11, 2 to 8, and 4% of the dose, respectively. As noted in the feces, many of the biliary metabolites have not been characterized. Excretion Data for lansoprazole are summarized in **Table 14**.

Species	Dose (mg/kg)	Route	Percent of the Carbon-14 Dose		
			Urine	Feces	Bile
Rat	2	po	17.9	81.0	
	2-D	po	16.7	81.5	
	2	id	13.2	20.8	59.6
Dog	2	po	12	83.7	
	0.5	po	24.6*	67.5	
	0.5	iv	28.4*	63.9	
	0.5	iv			42.6
Human	ca. 0.43	po	32.2	64.3	

\* includes cagewash; D = daily dosing; po = orally dosed; iv = intravenously dosed; id = intraduodenally dosed

## In Humans

### **PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)**

#### Mechanism of action

Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or histamine H<sub>2</sub> antagonist properties, but that suppress gastric acid secretion by specific inhibition of the (H<sup>+</sup>,K<sup>+</sup>)-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. The inhibition of gastric acid secretion persists for up to 36 hours after a single dose. Thus, the plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion.

#### Antisecretory activity

After oral administration, lansoprazole was shown to significantly decrease the basal acid output, and significantly increase the mean gastric pH and percent of time the gastric pH was >3 and >4. Lansoprazole also significantly reduced meal-stimulated gastric acid output and secretion volume. Lansoprazole also significantly reduced pentagastrin-stimulated acid output. In patients with hyper secretion of acid, lansoprazole significantly reduced basal and pentagastrin-stimulated gastric acid secretion. Lansoprazole inhibited the normal increases in secretion volume, acidity and acid output induced by insulin.

In a crossover study comparing lansoprazole 15 and 30 mg to omeprazole 20 mg for 5 days, the following effects of lansoprazole on intragastric pH were noted (**Table 15**).

<b>Parameter</b>	<b>Baseline Value</b>	<b>Lansoprazole 15 mg</b>	<b>Lansoprazole 30 mg</b>	<b>Omeprazole 20 mg</b>
Mean 24-hour pH	2.05	4.03 <sup>+</sup>	4.91 <sup>*</sup>	4.16 <sup>+</sup>
Mean Nighttime pH	1.91	3.01 <sup>+</sup>	3.80 <sup>*</sup>	3.04 <sup>+</sup>
% Time Gastric pH >3	18	59 <sup>+</sup>	72 <sup>*</sup>	61 <sup>+</sup>
% Time Gastric pH >4	12	49 <sup>+</sup>	66 <sup>*</sup>	51 <sup>+</sup>

Note: An intragastric pH of >4 reflects a reduction in gastric acid by 99%

\* (p<0.05) versus baseline, lansoprazole 15 mg and omeprazole 20 mg

+ (p<0.05) versus baseline only

After the initial dose in this study, increased gastric pH was seen within 1 to 2 hours with lansoprazole 30 mg, 2 to 3 hours with lansoprazole 15 mg, and 3 to 4 hours with omeprazole 20 mg. After multiple daily dosing, increased gastric pH was seen within the first hour postdosing with lansoprazole 30 mg and within 1-2 hours postdosing with lansoprazole 15 mg and omeprazole 20 mg.

Higher levels of acid suppression have been predicted to potentiate the activity of antibiotics in eradicating *H. pylori*. The percentage of time gastric pH was elevated above 5 and 6 was evaluated in a crossover study of PREVACID® (lansoprazole delayed-release capsules) given q.d., b.i.d. and t.i.d. (Table 16).

Table 16 Mean Antisecretory Effects After 5 Days of b.i.d. and t.i.d. Dosing				
Parameter	PREVACID®			
	30 mg q.d.	15 mg b.i.d.	30 mg b.i.d.	30 mg t.i.d.
% Time Gastric pH >5	43	47	59 <sup>+</sup>	77 <sup>*</sup>
% Time Gastric pH >6	20	23	28	45 <sup>*</sup>
<sup>+</sup> (p<0.05) versus PREVACID® 30 mg q.d. <sup>*</sup> (p<0.05) versus PREVACID® 30 mg q.d., 15 mg b.i.d. and 30 mg b.i.d.				

The inhibition of gastric acid secretion as measured by intragastric pH returns gradually to normal over two to four days after multiple doses. There is no indication of rebound gastric acidity.

#### Other gastric and esophageal effects

Lansoprazole did not significantly affect mucosal blood flow in the fundus of the stomach. Due to the normal, physiologic effect caused by the inhibition of gastric acid secretion, a decrease of 17% in blood flow in the antrum, pylorus and duodenal bulb was seen. Lansoprazole did not significantly affect gastric emptying of liquids, but significantly slowed the gastric emptying of digestible solids. Esophageal motility and lower esophageal sphincter tone were not modified by lansoprazole therapy. Lansoprazole increased serum pepsinogen levels and decreased pepsin activity under basal conditions and in response to meal stimulation or insulin injection. In patients with gastric ulcer, increases in gastric pH were associated with increases in nitrate-reducing bacteria and elevation of nitrite concentration in gastric juice; however no significant increase in nitrosamine concentrations were observed.

### Enterochromaffin-like cell effects / Carcinoid formation

In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with doses of 5 to 150 mg/kg/day about 1 to 40 times the exposure on a body surface (mg/m<sup>2</sup>) basis, of a 50 kg person of average height (1.46 m<sup>2</sup> body surface area) given the recommended human dose of 30 mg/day (22.2 mg/m<sup>2</sup>). Lansoprazole produced dose-related gastric enterochromaffin-like (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats lansoprazole produced a dose related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg/kg/day (4 to 40 times the recommended human dose based on body surface area) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rats. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg/kg/day (13 times the recommended human dose based on body surface area) in a one year toxicity study. Hypergastrinemia secondary to prolonged and sustained hypochlorhydria, such as that induced by high doses of ranitidine, omeprazole, and surgery, has been postulated to be the mechanism by which ECL cell hyperplasia and gastric carcinoid tumors develop.

Gastric biopsy specimens from the body of the stomach from over 300 patients treated continuously with lansoprazole for eight weeks to 120 weeks have not shown evidence of ECL effects similar to those seen in rats. Longer term data are needed to rule out the possibility of an increased risk for the development of gastric carcinoid tumors in patients receiving long-term therapy with lansoprazole.

### Serum gastrin effects

Fasting serum gastrin levels increased modestly during the first two to four weeks of therapy with 15 to 60 mg of lansoprazole. This increase was dose-dependent. Median serum gastrin values in over 2100 patients treated with lansoprazole 15 to 60 mg remained within normal range and generally increased 1.5 to twofold. Gastrin values returned to pretreatment levels within four weeks after discontinuation of therapy.

### Endocrine effects

Human studies for up to one year have not detected any clinically significant effects on the endocrine system. Hormones studied included testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulphate (DHEA-S), prolactin, cortisol, estradiol, insulin, aldosterone, parathormone, glucagon, thyroid stimulating hormone (TSH), triiodothyronine (T<sub>3</sub>), thyroxine (T<sub>4</sub>), and somatotrophic hormone (STH). Lansoprazole oral doses of 15 to 60 mg for up to one year had no clinically significant effect on sexual function. In addition, lansoprazole in oral doses of 15 to 60 mg for two to eight weeks had no clinically significant effect on thyroid function.

In 24-month carcinogenicity studies in Sprague-Dawley rats with daily dosages up to 150 mg/kg, proliferative changes in the Leydig cells of the testes, including benign neoplasm, were increased compared to control rats. These findings are rat specific.

#### Other effects

No systemic effects of lansoprazole on the central nervous system, lymphoid, hematopoietic, renal, hepatic, cardiovascular or respiratory systems have been found in humans. Lansoprazole in oral doses of 15 to 60 mg for two to eight weeks, had no clinically significant effect on thyroid function. No PREVACID<sup>®</sup>-related visual adverse events were noted in over 7000 patients treated in Phase I to Phase III clinical trials worldwide. No visual toxicity was observed among 63 patients who had extensive baseline eye evaluations, were treated with up to 180 mg/day of lansoprazole and were observed for up to 68 months. Other rat-specific findings after a lifetime exposure included focal pancreatic atrophy, diffuse lymphoid hyperplasia in the thymus, and spontaneous retinal atrophy.

#### **BIAXIN<sup>®</sup> BID (clarithromycin tablets, USP, film-coated)**

##### *Helicobacter pylori*

The presence of *H. pylori* may damage the mucosal integrity and defenses so that exposure to acid/pepsin, even in normal concentrations, produces ulceration.

*H. pylori* displays potent urease activity which may produce an alkaline environment around the organism. Excess ammonia produced by urea hydrolysis is toxic to mucosal cells and may lead to parietal cell failure and/or to a disturbance of the normal negative feedback of acid to the antral G-cells which secrete gastrin. In addition, *H. pylori* produces catalases, lipases, phospholipases, proteases, adhesins and toxins. These enzymes may further degrade the mucous layer and damage the epithelial cell membrane. Also, the presence of *H. pylori* stimulates an active inflammatory response which contributes to mucosal damage.

Gustavson *et al.* (1995) showed that concentrations of 39.3, 23.1 mcg/g and 25.2 mcg/g clarithromycin were achieved in the gastric mucosa 2, 4, and 6 hours respectively after administering 500 mg clarithromycin t.i.d. and that corresponding concentrations of the 14 hydroxy-metabolite were 3.2, 1.1, and 4.1 mcg/g respectively. Similar results were obtained whether or not clarithromycin was given alone or together with 40 mg omeprazole once daily (Logan *et al.*, 1995). Although the activity of the hydroxy metabolite is about half of the parent drug and its concentrations are lower, it may still contribute antibacterial activity.

## AMOXICILLIN (amoxicillin trihydrate) Capsules

Amoxicillin is stable in the presence of gastric acid. Amoxicillin is rapidly and well absorbed after oral administration to fasting subjects. It was found in a recent study that peak serum antibiotic levels were reduced by 50% in subjects receiving amoxicillin immediately following a standard meal. Reducing the dose–water volume given with amoxicillin from 250 to 25 mL in fasted subjects also caused a significant reduction in serum amoxicillin levels. This may be due to the low water solubility of amoxicillin trihydrate (1 g in 370 mL water). In addition, food ingestion immediately before dosing also reduced the urinary excretion.

Peak serum levels are attained between 1 and 2 hours after drug administration. Amoxicillin diffuses readily into most body tissues and fluids, with the exception of brain and spinal fluid. Amoxicillin is excreted largely unchanged in the urine while 10 to 25% of the administered dose is excreted in the form of penicilloic acid. The excretion of amoxicillin can be delayed by concurrent administration of probenecid. Amoxicillin is not highly protein bound. In blood serum, amoxicillin is approximately 17 to 18% protein bound compared to 59% for penicillin G.

The following amoxicillin mean serum levels were found following the administration of 250 mg capsules of Amoxicillin to 12 healthy adult volunteers:

Time (hr.)	0.5	1	1.5	2	3	4	5	7
Mean Serum Levels (mcg/mL)	0.81	2.96	3.17	3.1	2.22	1.12	0.5	0.11

Peak blood serum levels averaged 3.8 mcg/mL (range 2.35 to 6.38) and the  $T_{max}$  was 1.50 hr. The mean biological half–life ( $t_{1/2}$ ) was found to be 55.8 minutes with a mean elimination rate constant  $K_{el}$  of 0.7456  $hr^{-1}$ .

Twelve normal male subjects participated in a bioavailability study of Amoxicillin Granules for Suspension. Each subject was given 5 mL (250 mg) of reconstituted Amoxicillin Granules for Suspension in a single dose.

The following amoxicillin mean serum levels were found:

Time (hr.)	0.5	1	1.5	2	3	4	5	7
Mean Serum Levels (mcg/mL)	3.26	4.19	3.4	2.56	1.65	0.98	0.43	0.1

Peak plasma concentrations from 2.65 to 5.75 mcg/mL were obtained with a mean  $C_{max}$  of  $4.24 \pm 0.74$  mcg/mL. The time required to reach peak concentrations ranged from 0.5 to 1.5 hours, with a  $T_{max}$  mean of  $1.00 \pm 0.21$  hr.

The AUC's calculated for 0 to 7 hours ranged from 8.475 to 12.865 mcg–hours/mL. The mean AUC was  $10.713 \pm 1.443$  mcg–hours/mL. The mean biological half-life for Amoxicillin Granules for Suspension was 26.4 minutes. The mean elimination rate constant ( $K_{el}$ ) was  $1.57 \text{ hour}^{-1}$ .

The administration of 500 mg amoxicillin to healthy fasting subjects has been reported to produce peak mean serum levels of 10.8 mcg/mL and 6.75 mcg/mL. Additional studies in healthy volunteers with normal renal function receiving 500 mg doses, indicated that peak serum levels could vary from 5.0 to 10.8 mcg/mL. Serum amoxicillin half-life values reported in the literature vary from 1 to 1.3 hours. About 60 to 80% of an oral dose of amoxicillin is excreted in the urine. In the presence of renal impairment the serum half-life increases (between 7 and 10 hours), necessitating a reduction in the dosage administered.

## MICROBIOLOGY

### **BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

Clarithromycin exerts its antimicrobial action by binding to the 50S ribosomal subunit of susceptible microorganisms resulting in inhibition of protein synthesis.

Clarithromycin is active *in vitro* against various aerobic and anaerobic gram-positive and gram-negative organisms. Additionally, the 14-OH clarithromycin metabolite also has significant antimicrobial activity which may be additive to the activity of the parent compound.

Clarithromycin is bactericidal to *Helicobacter pylori*; this activity is greater at neutral pH than at acid pH.

#### *In vitro* Activity of Clarithromycin against *Helicobacter pylori*

Clarithromycin has demonstrated *in vitro* activity against *H. pylori* isolated from patients with duodenal ulcers. *In vitro* susceptibility testing methods (broth microdilution, agar dilution, E-test, and disk diffusion) and diagnostic products currently available for determining MICs and zone sizes have not been standardized, validated, or approved for testing *H. pylori*. The clarithromycin MIC values and zone sizes will vary depending on the susceptibility testing methodology employed, media, growth additives, pH, inoculum concentration tested, growth phase, incubation atmosphere, and time.

## Susceptibility Test for *Helicobacter pylori*

*In vitro* susceptibility testing methods and diagnostic products currently available for determining MICs and zone sizes have not been standardized, validated, or approved for testing *H. pylori* microorganisms. MIC values for *H. pylori* isolates collected during two U.S. clinical trials evaluating clarithromycin plus omeprazole, were determined by broth microdilution MIC methodology (Hachem CY *et al.*, 1996). Results obtained during the clarithromycin plus omeprazole clinical trials fell into a distinct bimodal distribution of susceptible and resistant clarithromycin MICs.

If the broth microdilution MIC methodology published in Hachem CY *et al.*, 1996 is used and the following tentative breakpoints are employed, there should be reasonable correlation between MIC results and clinical and microbiological outcomes for patients treated with clarithromycin plus omeprazole (see **Table 17**).

<b>Table 17</b> <b>Susceptibility Testing for <i>Helicobacter pylori</i> in Patients Treated</b> <b>With Clarithromycin and Omeprazole</b>	
<b>MIC (mcg/mL)</b>	<b>Interpretation</b>
≤0.06	Susceptible (S)
0.12 to 2.0	Intermediate (I)
≥4	Resistant (R)

These breakpoints should not be used to interpret results obtained using alternative methods.

## **TOXICOLOGY**

### **In Animals**

#### **PREVACID<sup>®</sup> (lansoprazole delayed-release capsules)**

##### **Single-Dose Studies**

In an acute toxicity study, lansoprazole administered via the oral (po), subcutaneous (sc) and intraperitoneal (ip) routes was studied in groups of 5M, 5F Wistar rats and 5M, 5F ICR mice. Lansoprazole was suspended in 5% gum arabic adjusted to pH 7 for administration by all three routes. The LD<sub>50</sub> by the po route in both rats and mice was greater than 5000 mg/kg, the highest dose tested. There were no deaths in either study. The only clinical sign noted was dark brown urine in mice.

By the sc route, the LD<sub>50</sub> was again greater than 5000 mg/kg, the highest dose tested. Again, there were no deaths in either species. Scratching at the injection site and abdominal stretching were observed in mice. There were no clinical signs in rats. Drug remnants were seen at the injection sites in both species.

Finally, when lansoprazole was administered via the ip route, there were no deaths in mice at 5000 mg, but several rats of both sexes died within two days after dosing. Surviving rats were normal by the second day after dosing. The LD<sub>50</sub> in rats was approximately 5000 mg. Abdominal stretching, decreases in activity, respiratory depression, and hypotonia of abdominal muscles were seen in rats and mice. Dark purple urine was also seen in mice. At autopsy, drug remnants were seen in the peritoneal cavity in animals of both species. Discoloration of the liver was also seen in rats that died at 5000 mg. These studies demonstrated that lansoprazole has a very low degree of toxicity when given as a single dose by either the oral, sc, or ip routes.

In an acute toxicity study of several metabolites, a contaminant, and partially degraded lansoprazole (40°C and 75% relative humidity for six months) were determined in ICR mice. The compounds and the routes tested were pyridyl-N-oxide derivative (po), sulfonyl derivative or metabolite VII (po and ip), thio derivative or metabolite I (po and ip), 5-hydroxy derivative or metabolite VI (ip), and partially degraded lansoprazole (po). There were no deaths, and the LD<sub>50</sub> values in all cases were therefore greater than 5 g/kg, the limit dose. With oral administration, clinical signs were seen only with partially degraded lansoprazole. These included decreased activity, respiratory depression, hypo-irritability (decreased responsiveness), ataxia, and flattened posture (prostration). With ip administration, decreased activity, hypo-irritability, and respiratory depression were seen with metabolites VI and VII. In addition, with metabolite VII, chromaturia (dark purple urine) and soft feces or diarrhea were seen. These findings are all similar to the results of previous acute toxicity studies with lansoprazole. Therefore, none of the tested compounds were more toxic than lansoprazole itself.

In a single-dose study, two male beagle dogs per group (fasted for 18 hours) were given lansoprazole orally by gavage at doses of 500, 1000, and 2000 mg/kg. The drug was suspended in 5% gum arabic, pH 7. The dogs were observed for 15 days after dosing and subjected to necropsy. Organ weights and histopathologic assessments of selected organs were obtained. There were no deaths, no treatment-related clinical signs, no effects on body weight or food consumption, no effects on weights of major organs, and no treatment-related gross or histopathologic changes. Therefore, a single dose of 2000 mg/kg was non-toxic. Higher dosing was not justified for humane reasons.

### Multidose Studies

In a three-month study, lansoprazole was given by oral gavage to groups of ten male and ten female CD-1 mice at dosages of 0, 15, 50, and 150 mg/kg/day. The vehicle was 5% gum arabic. Clinical signs, body weight, and food consumption were monitored. At the end of the study, blood was collected for hematology and biochemistry measurements. All animals were necropsied. Histologic evaluations were conducted on high-dosage and control animals, and stomachs were evaluated histologically in all animals.

There were no treatment-related deaths and no effects on clinical signs, body weight, food consumption, hematology, or serum chemistry variables. There were no treatment-related gross pathologic changes. Stomach weights were increased, and hyperplasia/hypertrophy of the glandular stomach was seen histologically at 50 and 150 mg/kg/day. These changes were secondary to the pharmacologic activity of the compound.

In a 13-week study, lansoprazole was given by oral gavage to groups of 10 male and 10 female CD-1 mice at dosages of 0, 150, 300, 600, 1200, and 2400 mg/kg/day. The drug was suspended in 5% gum arabic, pH 7. There were three possibly drug-related deaths at 2400 mg/kg/day. The only clinical sign observed was purple urine seen in all drug-treated groups. There were slight decreases (approximately 10 to 13% relative to controls) in hematocrit, hemoglobin, and erythrocyte counts in all drug-treated groups. Neutrophils were slightly decreased in drug-treated females. Total serum protein was decreased at 300 mg/kg/day or more. Stomach weights were increased in all drug-treated groups. Liver weights were increased at 300 mg/kg/day or more. Testis weights were decreased at 1200 and 2400 mg/kg/day. At necropsy, the glandular stomach appeared thickened, and erosions of the mucosa were evident at all dosages. The testes appeared small at 1200 and 2400 mg/kg/day. Histologically, hyperplasia and vacuolation were seen in the gastric fundic mucosa in all drug-treated groups. A mild, chronic gastritis was seen at 300 mg/kg/day or more. Hepatocellular hypertrophy and vacuolation were seen at 150 mg/kg/day or more, and a brown pigment was seen in the liver mainly at 2400 mg/kg/day. Seminiferous tubular atrophy and aspermatogenesis were seen with increased incidence at 1200 and 2400 mg/kg/day. Reduced amount of sperm was seen in the epididymides at 1200 mg/kg/day or more. A no-toxic-effect dosage was not determined in this study. The MTD was judged to be in the range of 300 to 600 mg/kg/day.

In a three-month study, lansoprazole was administered by gavage to groups of 15 Sprague-Dawley rats/sex at dosages of 0, 5, 15, 50, and 150 mg/kg/day seven days per week. The drug was suspended in 5% gum arabic, pH 7.

There were no deaths and no behavioural signs of toxicity. Body weight was decreased in males at 150 mg/kg/day. There was no effect on food consumption. Hemoglobin and mean cell hemoglobin were decreased in females at 50 mg/kg/day or more, and in males at 150 mg/kg/day. Hematocrit was also decreased in males and females, and mean erythrocyte volume was decreased in males at 150 mg/kg/day. Total leukocyte counts were increased in females at 50 mg/kg/day or more. Serum total protein and globulin were decreased, and A/G ratio increased in males at 150 mg/kg/day. There were no gross lesions noted at necropsy. Stomach weight was increased at 15 mg/kg/day or more. Liver weights were increased in females at 15 mg/kg/day or more. Thyroid and uterus weights were increased at 150 mg/kg/day. Thymus weights were decreased at 50 mg/kg/day or more. Histologically, thymic atrophy was observed at 15 mg/kg/day or more. In the stomach, increased chief cell hypertrophy, eosinophilia and single cell necrosis, eosinophilic material in gastric glands, and increased squamous cell hyperplasia and hyperkeratosis at the junction of the glandular and non-glandular mucosa were observed at 50 mg/kg/day or more.

Toxicity was demonstrated by decreased body weight in males, hematologic changes, decreases in serum protein, thymic atrophy, and chief cell necrosis. Hematologic changes and chief cell necrosis occurred at 50 mg/kg/day or more. Thymic atrophy was observed at 15 mg/kg/day or more. Therefore, the no-toxic-effect dosage was 5 mg/kg/day.

In a four-week study, lansoprazole was administered orally by gavage to ten Wistar rats/sex/group at dosages of 0, 15, 50, and 150 mg/kg/day (seven days/week). The drug was suspended in 5% gum arabic for administration.

There were no deaths and no behavioural signs of toxicity. Body weight gain was suppressed in males by 7% at 50 mg/kg/day and by 15% at 150 mg/kg/day. Food consumption was decreased in both sexes at 150 mg/kg/day and in males at 50 mg/kg/day. Hepatic drug-metabolizing enzymes, aminopyrine-N-demethylase and aniline hydroxylase activities, were increased at 150 mg/kg/day. Thymic atrophy was noted at necropsy at 150 mg/kg/day. Thymic weights were decreased 21 to 27% at 50 mg/kg/day and 48 to 49% at 150 mg/kg/day. Liver weights were increased at 50 and 150 mg/kg/day. Adrenal weights were increased in females at 150 mg/kg/day. Histologically, centrilobular hepatocellular hypertrophy was seen in the liver at 150 mg/kg/day. An increase in smooth endoplasmic reticulum in the liver was seen by electron microscopy. In the stomach, vacuolation of parietal cells and apical eosinophilia of chief cells were seen histologically, while dilation of parietal cell tubulovesicles was seen by electron microscopy at 150 mg/kg/day.

Toxicity was demonstrated by decreases in body weight gain and food consumption, and thymic atrophy at 50 mg/kg/day or more. The no-toxic-effect dosage was 15 mg/kg/day.

In a 13-week study, lansoprazole was administered to Wistar rats (ten/sex/group) at dosages of 0, 5, 15, and 50 mg/kg/day, seven days/week. The drug was suspended in 5% gum arabic adjusted to pH 7.

There were no deaths and no behavioral signs of toxicity. Body weight was decreased 5 to 6% in both sexes by the end of the study at 50 mg/kg/day. There were no treatment-related effects on hematology, serum chemistry, or urinalysis variables. Measurements of plasma T<sub>3</sub>, T<sub>4</sub>, and TSH in the high-dosage and control animals revealed no differences between the two groups. Statistically significant elevations in serum gastrin, determined 20 hours post-dosing at the end of the study, were obtained in females at 15 mg/kg/day or more and in males at 50 mg/kg/day. At necropsy, the stomach glandular mucosa was observed to be thickened in both sexes at 50 mg/kg/day and in females at 15 mg/kg/day. Stomach weights were increased at all dosages.

Thymus and submaxillary weights were decreased at 50 mg/kg/day. Histologically, centrilobular hepatocellular hypertrophy was seen in the liver at 50 mg/kg/day. In the stomach, increased argyrophil cell density, hypertrophy of parietal cells, and sporadic necrosis of chief cells were seen at 50 mg/kg/day. Chief cell eosinophilia, hypertrophy, and hyperplasia were seen at all dosages. Dilation of tubulovesicles in parietal cells and small, dense granules in chief cells were seen by electron microscopy at 50 mg/kg/day.

Toxicity was demonstrated by decreased body and thymus weights and chief cell necrosis at 50 mg/kg/day. The no-toxic-effect dosage was 15 mg/kg/day.

In a 13-week study, male Wistar rats were given daily dosages of 50 mg/kg/day lansoprazole orally by gavage, and were then allowed to recover without treatment for periods of four, 13, or 26 weeks. A control group was given vehicle (5% gum arabic, pH 7). There were ten rats for each of the necropsy intervals (13 weeks treatment, four weeks recovery, 13 weeks recovery, and 26 weeks recovery).

The changes observed at the end of 13 weeks of treatment were similar to those seen at 50 mg/kg/day in the previous 13-week study. In this study, gastrin-secreting cells (G cells) were determined in the stomach pylorus by immunohistochemical staining. The volume density of G cells was found to be increased after 13 weeks of treatment. All of the changes were found to be reversible after four weeks recovery without treatment except stomach weight, changes in chief cells, and the increase in argyrophil cells. The increase in argyrophil cells was reversible after 13 weeks of recovery. Necrosis, eosinophilia, hypertrophy, and hyperplasia of chief cells showed partial reversal after four and 13 weeks recovery and complete reversal after 26 weeks, recovery. Stomach weight in the treated group was comparable to controls after 26 weeks of recovery.

In a six-month study, lansoprazole was given to Sprague-Dawley rats (12/sex/group) at dosages of 0, 2, 10, and 50 mg/kg/day, seven days/week. The drug was suspended in 5% gum arabic, pH 7, and administered orally by gavage.

There were no treatment-related deaths, no behavioral signs of toxicity, no effects on body weight or food consumption, and no treatment-related changes in serum chemistry or urinalysis variables. There was a transient decrease in hematocrit, mean erythrocyte cell volume, and mean erythrocyte cell hemoglobin at 50 mg/kg/day after three months of treatment. This was not seen at the end of the study. Stomach weight was increased in females at all dosages and in males at 10 mg/kg/day or more. Thymus weights were decreased at 50 mg/kg/day. Histologically, thymic atrophy was seen at 10 mg/kg/day or more. In the stomach, increased hypertrophy, eosinophilia, and single cell necrosis of chief cells and an increase in argyrophil cells were seen at 10 mg/kg/day or more. At 50 mg/kg/day, dilation of gastric glands and increased severity of inflammatory cell accumulation, squamous cell hyperplasia, and hyperkeratosis at the junction of the glandular and nonglandular mucosa were seen.

Toxicity was demonstrated by the hematologic changes at 50 mg/kg/day, thymic atrophy at 10 mg/kg/day or more, and chief cell necrosis at 10 mg/kg/day or more. The no-toxic-effect dosage was 2 mg/kg/day.

In a one-year study, lansoprazole was administered by oral gavage to Sprague-Dawley rats (30/sex/group) at dosages of 0, 1.5, 5, 15, and 50 mg/kg/day, seven days per week. The vehicle was 5% gum arabic adjusted to pH 7.

There were no treatment-related deaths and no behavioral signs of toxicity. Body weight gain was decreased in males at 50 mg/kg/day, but there was no effect on food consumption. Hematocrit and hemoglobin were decreased at 50 mg/kg/day. There were no treatment-induced changes in serum chemistry or urinalysis variables. Stomach weight was increased at 5 mg/kg/day or higher. Liver weight was increased in females, while thymus weight was decreased in males at 50 mg/kg/day. Histologic evidence of thymic atrophy was also seen at 50 mg/kg/day. In the stomach, hypertrophy, eosinophilia and necrosis of chief cells was seen at 5 mg/kg/day or more. Dilated gastric glands and increased incidence of argyrophil cells were seen at 15 mg/kg/day or more. Increased severity of inflammatory cells, squamous hyperplasia, and hyperkeratosis at the junction of the glandular and nonglandular mucosa was seen at 50 mg/kg/day. In the testis at 50 mg/kg/day, an increased incidence of Leydig (interstitial) cell hyperplasia was observed, and a single, benign Leydig cell tumor was found.

Toxicity was characterized by decreased body weight gain in males, decreases in hematocrit and hemoglobin, thymic atrophy, and Leydig cell hyperplasia at 50 mg/kg/day and by chief cell necrosis at 5 mg/kg/day or more. The no-toxic-effect dosage was 1.5 mg/kg/day.

In a six-month study, lansoprazole was given to four beagle dogs/sex/group in hard gelatin capsules at dosages of 0, 2, 10, and 50 mg/kg/day seven days per week.

There were no deaths or behavioral signs of toxicity. There were no treatment-related effects on body weight, food consumption, urinalysis, or ophthalmologic, electrocardiographic, or serum chemistry variables. One dog in the high-dosage group had a few atrioventricular (A-V) nodal escape beats; however, this sometimes occurs spontaneously in dogs and was not considered treatment related either by the sponsor or a consulting veterinary cardiologist. There were transient (present at three months but not at six months) decreases in hematocrit, hemoglobin, and erythrocyte counts in males at 2 and 10 mg/kg/day. Hematocrit, hemoglobin, mean cell hemoglobin, and mean erythrocyte volume were persistently decreased at both three and six months at 50 mg/kg/day in males. Total leukocyte count was increased in females at 50 mg/kg/day. There were no treatment-related findings at necropsy. Thymus weight was decreased in males at 50 mg/kg/day. Histologically, increased vacuolation of parietal cells in the gastric mucosa was seen at 10 mg/kg/day or more.

Toxicity was characterized by hematologic changes and by decreased thymus weights at 50 mg/kg/day. The no-toxic effect dosage was 10 mg/kg/day.

In a 12-month study, Beagle dogs were given lansoprazole in hard gelatin capsules at dosages of 0, 1.5, 5, 15, and 50 mg/kg/day, seven days per week. There were four dogs/sex/group. There were two deaths, one male each at 15 and 50 mg/kg/day.

In surviving dogs, there were no behavioral signs of toxicity, no effects on body weight or food consumption, no treatment-related ophthalmoscopic findings, and no effects on serum chemistry or urinalysis variables. There were no ECG abnormalities in any of the dogs in the study. Total leukocyte counts were increased at 15 and 50 mg/kg/day; the increase at 15 mg/kg/day was transient (present at three months but not at later intervals) and in males only. Prostate weight was decreased at 5 mg/kg/day or more. Histologically, increased parietal cell vacuolization was seen at all dosages.

The cause of death or moribundity could not be determined for the two dogs that died. There were no indications from the other dogs in the study of any toxicity that could account for these deaths. Nevertheless, a conservative approach suggests that these two deaths be considered the result of toxicity due to drug treatment. Therefore, the no-toxic-effect dosage for this study was 5 mg/kg/day.

### **BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

#### Acute Toxicity

The acute toxicity of clarithromycin administered by a variety of routes, was studied in mice and rats. The median lethal dose by the oral route ranged from 2.7 to >5.0 g/kg. Acute toxicity did not differ markedly between sexes (see **Table 18**).

<b>Table 18</b>			
<b>Acute LD<sub>50</sub> values of Clarithromycin</b>			
<i>Species</i>	<b>Sec</b>	<b>Route</b>	<b>LD<sub>50</sub> value (g/kg)</b>
Mice	M	p.o.	2.74
	F	p.o.	2.7
	M	s.c.	>5.0
	F	s.c.	>5.0
	M	i.p.	1.03
	F	i.p.	0.85
	M	i.v.	0.17
	F	i.v.	0.2
Rats	M	p.o.	3.47
	F	p.o.	2.7
	M	s.c.	>5.0
	F	s.c.	>5.0
	M	o.p.	6.69
	F	i.p.	7.58

The primary signs of toxicity included reduction in activities, behaviours, weight gains, respiration rates and sedation. The emetic activity of clarithromycin prevented the determination of the lethal dose in dog.

The acute oral toxicity of clarithromycin in very young mice and rats was determined. The median lethal dose (1.2 g/kg) was about 2 fold that seen in the older rodents.

## Subchronic Toxicity

Studies were conducted in rats, dogs and monkeys with clarithromycin administered orally. The duration of administration ranged from 14 days to 42 days.

### *Rats*

One study in rats (with oral doses up to 800 mg/kg/day) failed to show adverse effects in rats exposed to 50 mg/kg/day for 4 weeks. The clinical signs observed at toxic doses were reduced motility, piloerection, hypothermia and perineal urine staining. Changes occurred in biochemical parameters at 200 and 800 mg/kg/day indicative of hepatotoxicity which was confirmed by histopathologic findings of hepatocyte necrosis.

Other pathologic findings at the top two dose levels included swelling of the renal cortical tubular epithelia and atrophic changes to the lymphatic and genital systems. The same toxicity profile was observed in immature rats following the daily administration of oral doses up to 150 mg/kg/day of clarithromycin for 6 weeks. At 150 mg/kg/day, there was an increase in relative weights of liver and kidneys.

### *Dogs*

Dogs were dosed orally with 0, 6.25, 25, 100 or 400 mg/kg/day of clarithromycin daily for 28 days. Emesis occurred sporadically in the treated dogs. No other adverse effects were seen in dogs exposed to 6.25 mg/kg/day. The clinical signs at higher dosages included loose stools, lacrimation and conjunctivitis.

Slight anorexia was noted in dogs receiving 100 mg/kg/day or more. Dogs at 400 mg/kg/day exhibited reduced red blood cell count, hematocrit, hemoglobin concentration, serum albumin, and mean urine pH and specific gravity. Increases were seen in serum transaminase, alkaline phosphatase, and total bilirubin concentrations.

Bilirubin was detected in the urine. Other pathologic changes at 400 mg/kg/day included biliary hyperplasia, gastric glandular atrophy, renal tubule epithelial atrophy, edema of the iris, ciliary body and choroid, capillary proliferation in the cornea, suppression of spermatogenesis, and adrenal medullary degeneration.

### *Monkeys*

Monkeys were treated daily for one month with oral doses of 0, 25, 100 or 400 mg/kg/day. Two animals out of ten receiving 400 mg/kg/day died. Salivation was recorded at all dosage levels. No other adverse effects were seen in animals treated daily with 25 mg/kg/day.

The clinical signs observed at higher doses and most frequently at 400 mg/kg/day were vomiting, emesis, sunken eyes, dehydration, emaciation, low rectal temperature, body weight loss, reduced food consumption, cloudiness of the cornea and reduction in intra-ocular pressure. Yellow discoloured feces were passed on a few isolated occasions by some animals given a dose of 400 mg/kg/day. As with the other species, the liver was the primary target at toxic doses as shown by early elevation of serum concentration of glucose, BUN, creatinine, ALT, AST, LDH, amylase and/or triglyceride; an electrolyte imbalance and low levels of protein, cholesterol, phospholipid; elevated leucine aminopeptidase (LAP).

Principal histopathologic changes were seen mainly in high dose monkeys, but some mid-dose monkeys exhibited similar alterations. Changes included, necrosis and vacuolation of hepatocytes, vacuolation of renal cortical tubules, no spermatogenesis, thymic regression and single cell necrosis of the stomach. In man the recommended dose is 500 to 1000 mg/day or 7.1 to 14.3 mg/kg/day (70 kg person).

### Chronic Toxicity

Rats (20/sex/group) were treated daily with oral doses of 0, 15, 37.5, 75 or 150 mg/kg/day for three months. There were eight incidental deaths, but none of them were considered treatment related. Clinical signs included increased salivation, dehydration, hyperactivity and were observed in a dose-related manner. The only toxic effect noted, was some variation in body weight gain. No toxicologically significant changes occurred in hematology, biochemistry or urinalysis results.

Post mortem, there was an increase in mean relative liver and kidney weights at the top dose level. No microscopic changes were detected in the kidneys, but in the liver, there was a sex/dose-related increase in multinucleated hepatocytes. Effects were only seen in females at 150 mg/kg/day but in males occurred as low as 37.5 mg/kg/day.

A six-month oral study was performed in rats (20 to 27/sex/group) at dosages of 0, 1 to 6, 8, 40 or 200 mg/kg/ day. Seven male and female rats from the control group and the 40 and 200 mg/kg/day groups were allowed a 63-day non-dosed recovery period. No mortalities occurred. Body weight and food intake were reduced at high doses during the dosing phase but normalized during recovery.

Water intake and urine volume increased in males and females of the 40 and 200 mg/ kg/day groups. Dose-related hematological changes included reduced erythrocytes and HCT with increased MCV, MCH and MCHC and relative eosinophil counts. Biochemical changes were mainly restricted to the high dose group and included increased ALP and decreased phospholipids; decreased total cholesterol and triglycerides, and increased AST and ALT in males only and decreased albumin in females only.

Organ weight increases were found to include cecum, adrenals, liver, and spleen. Histopathological examinations showed drug-related, recovery-reversible, increases in multinucleated hepatocytes associated with minimal and focal necrosis in livers of both sexes at the top two dose levels. No relevant pathology was found in the cecum, adrenals or spleen to account for the increased weights. After recovery only the 200 mg/kg/day group had increased multinucleated hepatocytes.

Dogs (7/sex/group) were administered daily with oral doses of 0, 10, 30, or 100 mg/kg/day of clarithromycin for three months. Emesis occurred at levels of 30 mg/kg and above. One male high dose dog was killed *in extremis* on day 69. Drug-related lesions were seen in the liver, gall bladder, thymus and stomach.

Hematological and biochemical changes at the high dose level included, decreased RBC and HCT, increased ALT, ALP, GGT, and decreased total protein and albumin. No significant organ weight changes were recorded, but treatment-related microscopic alterations in the liver and stomach of mild and high dose dogs were seen, as well as changes in gall bladder, spleen and thymus of high dose animals.

A six month oral study was also performed in dogs (4 to 5/sex/group) at dosages of 0, 0.8, 4, 20 or 100 mg/kg/day. At the 0 and 100 mg/kg levels, one male and one female dog were allowed a one-month, non-dosed, recovery period. One male high dose dog died on day 174. This death was considered to be as a direct result of clarithromycin administration. Histopathologic examination revealed hepatic parenchymal damage, identifying the cause of clinical jaundice. Clinical signs during the dosing phase of the study were restricted to the top two dose levels and included emesis and ocular signs. Food consumption and water intake were reduced at 20 and 100 mg/kg/day.

Hematologic changes at 100 mg/kg were indicative of subclinical anemia. Biochemical alterations at the same level were associated with liver damage. Ocular changes were only apparent at the top dose level.

Increase in the weights of lung, liver, spleen, adrenals and kidneys were found at 100 mg/kg/day. Histopathologic examination of these organs showed degeneration of liver parenchyma, and toxic effects in adrenals. The thymus weight was reduced at 100 mg/kg/day. At the end of the recovery period all findings had regressed or reduced.

Monkeys (5 to 6/sex/group) were similarly administered clarithromycin at levels of 0, 25, 50 or 100 mg/kg/day for six months. At the 0 and 100 mg/kg levels, one male and one female monkey were allowed a one-month recovery period. One high dose female died in week 25. Inhalation of vomit was considered to be the cause of death. Clinical signs were restricted to a dose-related incidence of emesis and salivation. No treatment-related effects were found in food consumption, ophthalmoscopy or hematology. Weight loss was restricted to one high dose female. Minor serum chemistry changes were seen at the 100 mg/kg level, particularly in plasma proteins. Urinalysis revealed a dose-related lowering of pH and SG at 13 weeks only. Organ weight increases in liver, adrenal and kidneys were seen at high doses, but pathology was

restricted to minimal liver changes consisting of cytoplasmic rarefaction of centrilobular hepatocytes. All changes were reversed during the recovery period.

### **AMOXICILLIN (amoxicillin trihydrate) Capsules**

#### Acute Toxicity

The following LD<sub>50</sub> values for amoxicillin expressed in mg/kg of body weight have been reported.

<b>Table 19</b>			
<b>Acute LD<sub>50</sub> Values for Amoxicillin (mg/kg)</b>			
	<b>Route of Administration</b>		
	<b>P.O.</b>	<b>I.P.</b>	<b>S.C.</b>
Mouse	>10,000	4350	>6,000
Rat	>8,000	4900	>6,000
Dog	>3,000	-	-

#### Subacute Toxicity

##### *Rats*

In one study male and female rats were orally administered 500 mg/kg amoxicillin daily for 21 days. With the exception of significantly greater ( $p < 0.01$ ) BUN values in the female test group compared with controls, there were no toxic effects on the organs, tissues or fluids of the body, nor any adverse effects on food consumption, weight gain, or efficiency of food utilization reported in the study.

Histopathologic evaluation of tissues revealed a minimal degree of fatty change in livers of treated females. However, this finding was not considered a toxic change but related to a possible alteration in the intestinal flora.

##### *Dogs*

One male and one female dog were dosed orally with 250 mg/kg amoxicillin daily for 14 days. During the period of observation, no deaths occurred, no adverse changes in body weight and no effect on food consumption was found. Laboratory values were found within normal limits. At post-mortem, no gross or microscopic abnormalities were reported and organ weights were within normal limits.

## Chronic Toxicity

### *Rats*

In one study male and female rats were given oral doses of 200, 500 and 2000 mg/kg/day amoxicillin, 6 days a week for 26 weeks. No apparent disturbances in absolute organ weights of either treated male or female animals were noted nor was any histologic evidence of response to treatment observed.

In another study, 3 groups of Sprague–Dawley rats were given oral doses of 200, 500 and 2000 mg/kg of amoxicillin for a test period of 13 to 15 weeks. There were no gross or histologic changes observed in the treated rats that were considered related to the administration of amoxicillin. Some of the intermediate and low–dose groups were shown to exhibit body weight gains lower (males) or slightly higher (females) than those of the control animals.

### *Dogs*

It has been reported that amoxicillin was administered orally at doses of 200, 500 and 2000 mg/kg/day to male and female dogs for a period of 6 months. (Groups consisted of 6 male and 6 female dogs initially, but after 3 months dosing, each group was reduced to 3 dogs).

During the first six weeks of treatment, occasional bouts of vomiting, one to four hours after dosing, were reported in dogs receiving 2000 mg/kg/day and 4 bouts of vomiting were recorded in dogs receiving the intermediate dose of 500 mg/kg/day. Grey coloured feces were seen on very isolated occasions in dogs treated at high and intermediate dose levels only. On seven occasions it involved dogs receiving the highest dose level (2000 mg/kg/day) and on three occasions dogs receiving the intermediate dose level (500 mg/kg/day).

Body weight gains of treated males were reported to be not significantly different from those of controls, but all dosed females increased in weight at a significantly slower rate than did the controls. This factor was reported to be attributable to excessive weight gain in the control animals. Food and water consumption was not affected. No abnormalities of the eyes were observed attributable to amoxicillin.

In a second study 2 groups of Beagle dogs were given oral doses of 500 mg/kg and 200 mg/kg of amoxicillin for 13 weeks. There were no gross or histologic changes reported in the treated dogs that were considered related to the administration of amoxicillin.

## **Carcinogenesis**

### **PREVACID® (lansoprazole delayed-release capsules)**

In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with doses of 5 to 150 mg/kg/day about 1 to 40 times the exposure on a body surface (mg/m<sup>2</sup>) basis, of a 50 kg person of average height (1.46 m<sup>2</sup> body surface area) given the recommended human dose of 30 mg/day (22.2 mg/m<sup>2</sup>). Lansoprazole produced dose-related gastric enterochromaffin-like (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats lansoprazole produced a dose related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg/kg/day (4 to 40 times the recommended human dose based on body surface area) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rats. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg/kg/day (13 times the recommended human dose based on body surface area) in a one year toxicity study.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with doses of 15 to 600 mg/kg/day, 2 to 80 times the recommended human dose based on body surface area. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. Lansoprazole also induced a low, non-dose-related incidence of carcinoid tumours in the gastric mucosa in several dose groups (one female mouse in the 15 mg/kg/day group, one male mouse in the 150 mg/kg/day group, and 2 males and 1 female in the 300 mg/kg/day group). It also produced an increased incidence of liver tumours (hepatocellular adenoma plus carcinoma). The tumour incidences in male mice treated with 300 and 600 mg/kg/day (40 to 80 times the recommended human dose based on body surface area) and female mice treated with 150 to 600 mg/kg/day (20 to 80 times the recommended human dose based on body surface area) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg/kg/day (10 to 80 times the recommended human dose based on body surface area).

Analysis of gastric biopsy specimens from patients after short-term treatment of proton pump inhibitors have not detected ECL cell effects similar to those seen in animal studies. Longer term studies in humans revealed a slight increase in the mean ECL-cell density, although there was no microscopic evidence of cell hyperplasia. Similar results were seen in the maintenance treatment studies, where patients received up to 15 months of lansoprazole therapy. Serum gastrin values increased significantly from their baseline values but reached a plateau after two months of therapy. By one month post-treatment, fasting serum gastrin values returned to lansoprazole therapy baseline. Moreover, results from gastric biopsies from short-term, long-term and maintenance treatment studies indicate that there are no clinically meaningful effects on gastric mucosa morphology among lansoprazole-treated patients.

In a two-year study, lansoprazole was administered by oral gavage to Sprague-Dawley rats (60 males and 60 females per group) at dosages of 0, 1.5, 5, 15, and 50 mg/kg/day five days per week. Drug was suspended in 5% gum arabic (adjusted to pH 7.0 to 7.4).

Survival rates were 27 to 33% in males and 30 to 45% in females. The median survival time was 650 days in males and 683 days in females. Body weight gain was decreased at 50 mg/kg/day in both sexes and at all dosages in females. At the end of the study, body weight gains for high-dose males and females were both decreased 20% compared to controls. There were no other clinical signs of toxicity.

The incidence of interstitial (Leydig) cell hyperplasia was increased above concurrent and historical control levels at dosages of 15 and 50 mg/kg/day. The incidence of Leydig cell tumors was increased above concurrent control levels at 15 mg/kg/day and was at the high end of the historical control range at 50 mg/kg/day. The increases in incidence of Leydig cell hyperplasia and tumors were statistically significant at 15 and 50 mg/kg/day when compared to concurrent controls. Histologically, the Leydig cell tumors appeared similar to those that occur spontaneously in Sprague-Dawley rats and in aging Fischer 344 rats.

There were numerous changes in the gastric mucosa indicative of the pharmacologic effect of lansoprazole that were similar to those seen in previous toxicity studies. This included necrosis of chief cells which was seen at 5 mg/kg/day or more. A small increase in incidence of intestinal metaplasia was seen in both sexes at 50 mg/kg/day. Detailed examination of the intestinal metaplasia foci revealed the presence of Paneth cells, indicating complete type intestinal metaplasia in virtually every case. A single, carcinoid tumor was seen in the gastric fundic mucosa in a female at 50 mg/kg/day.

The decreases in body weight gain, necrosis of chief cells, and increased incidence of Leydig cell hyperplasia and tumors demonstrated that a MTD was administered.

The results suggest that oral administration of lansoprazole at dosages of 15 and 50 mg/kg/day for two years leads to higher levels of interstitial (Leydig) cell hyperplasia and tumors than found in control rats. There was no evidence for any other tumorigenic response due to drug administration.

### **BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of clarithromycin.

### **AMOXICILLIN (amoxicillin trihydrate) Capsules**

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of amoxicillin. Studies to detect mutagenic potential of amoxicillin alone have not been conducted.

## **Mutagenicity**

### **PREVACID® (lansoprazole delayed-release capsules)**

Lansoprazole was not mutagenic in *in vitro* *Salmonella typhimurium* and *Escherichia coli* assays. A mouse micronucleus test at up to 5000 mg/kg (approximately 10,000 times the human dose) was negative for the induction of micronuclei. Results from a rat *in vivo/in vitro* unscheduled DNA synthesis assay in rat hepatocytes was negative. Also, a mammalian cell mutagenesis assay was negative.

*In vitro* cytogenetics studies showed increased levels of aberrations consisting mainly of chromatid breaks which occurred only at cytotoxic concentrations. These cytotoxic concentrations were at least 50 to 60 times expected clinical blood levels of parent drug. Therefore, such concentrations will not be used in humans.

### **BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

The following *in vitro* mutagenicity tests have been conducted with clarithromycin: *Salmonella*/mammalian microsome test, bacterial induced mutation frequency test, *in vitro* chromosome aberration test, rat hepatocyte DNA synthesis assay, mouse lymphoma assay, mouse dominant lethal study, mouse micronucleus test.

All tests had negative results except the *in vitro* chromosome aberration test which was weakly positive in one test and negative in another. In addition, a Bacterial Reverse-Mutation Test (Ames Test) has been performed on clarithromycin metabolites with negative results.

### **AMOXICILLIN (amoxicillin trihydrate) Capsules**

Long-term studies in animals have not been performed with amoxicillin.

## **Reproduction and Teratology**

### **PREVACID® (lansoprazole delayed-release capsules)**

Six separate studies covering all phases of the reproductive process have been conducted. Treatment with lansoprazole caused a dose related reduction of implantations, viable fetuses and live births, and caused delayed parturition at 150 mg/kg/day.

However, lansoprazole at oral doses up to 150 mg/kg/day (40 times the recommended dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

In two teratology studies, lansoprazole at dosages up to 300 mg/kg/day (approximately 600 times the human dose) was administered to rats on Days 6 to 17 of pregnancy. At higher dosages (150 to 300 mg/kg/day), only decreased fetal body weights were observed. Also at higher dosages, reduced ossification of vertebrae was indicative of fetal toxicity.

In rabbits, doses of lansoprazole up to 30 mg/kg/day (approximately 60 times the human dose) were administered on Days 6 to 18 of pregnancy. A treatment-related effect on fetal mortality at 30 mg/kg/day was noted, but there were no treatment related external, skeletal, or visceral abnormalities.

Lansoprazole is not considered to be teratogenic.

### **BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

Fertility and reproduction studies have shown that daily doses of 150 to 160 mg/kg/day to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring. Plasma levels in rats after 150 mg/kg/day were 2 times the human serum levels.

In the 150 mg/kg/day monkey studies, plasma levels were 3 times the human serum levels. When given orally after 150 mg/kg/day, clarithromycin was shown to produce embryonic loss in monkeys. This effect has been attributed to marked maternal toxicity of the drug at this high dose.

In rabbits, *in utero* fetal loss occurred at an intravenous dose of 33 mg/sq m, which is 17 times less than the maximum proposed human oral daily dose of 618 mg/sq m.

### **AMOXICILLIN (amoxicillin trihydrate) Capsules**

#### *Rats*

Daily doses of 200 and 500 mg/kg amoxicillin were administered orally in one reported study. Male rats that had attained a minimum age of 40 days were treated for 63 days and sexually mature females for 14 days prior to mating. Dosing continued throughout the remainder of the investigation. The duration of gestation was unaffected by treatment at either dosage. It was noted that pregnancy rate at 500 mg/kg was slightly lower than that of controls at the first and second matings. At 200 mg/kg, the pregnancy rate was essentially comparable to control values at both matings. The chronologic sequence of mating was comparable for all groups; at 500 mg/kg the total number of animals showing evidence of mating was slightly lower than that of controls at both pairings. Pre- and post- implantation losses were comparable for all groups at the first and second pregnancies.

Among the rats allowed to rear their young, litter sizes, litter weights, mean pup weights and the pup mortality rates for the group dosed at 500 mg/kg amoxicillin were comparable to control values at birth, 4 and 21 days postpartum. Mean pup weights and pup mortality rates were similarly unaffected by 200 mg/kg amoxicillin; but litter sizes and litter weights were lower than control values from birth through lactation. These differences were considered to be unrelated to treatment. No abnormal young were observed.

### Effects on Pregnancy

#### *Mice*

It has been reported that amoxicillin administered at doses of 200, 500 and 2000 mg/kg/day orally during days 6–15 of pregnancy produced no obvious signs of reaction to treatment or deaths among parent animals. Body weight changes of pregnant dams were comparable for all groups, as was the pregnancy rate.

Fetal loss was significantly higher among all test groups than among controls. However, as implantation rates also tended to be higher at the 500 and 2000 mg/kg doses, litter sizes were only marginally, and not significantly, lower than the control value. Litter sizes and implantation rate also tended to lie at or above the upper limit of the laboratory range. Due to the latter factors, the biologic importance of the increased fetal loss was uncertain.

It was noted that mean pup weights were comparable for all groups. The distribution of skeletal variants was considered to be unaffected by treatment at any dosage. A significantly higher proportion of pups with cervical ribs was found in the 200 mg/kg dose group. Cervical rib and 14th rib are the prolongations of the transverse processes of the cervical or lumbar vertebrae. Supernumerary ribs have an incidence which depends on the strain of animals. Cervical ribs are not abnormalities and have no pathologic significance.

In this experiment the incidence of cervical ribs was 12% in control rats and 16% in the drug-treated groups if the three groups are calculated together. If the groups are considered individually, then in the lowest dose group (200 mg/kg) the incidence of cervical ribs was 24%, which is, statistically, significantly higher than in the controls. This finding was not considered to be drug related since at the 500 mg/kg dose level the incidence of cervical ribs was significantly lower than in controls. At the highest dose level (2000 mg/kg) the incidence of cervical ribs was 17%, similar to the controls. The incidence of visceral abnormalities was not significantly affected at any dose level.

#### *Rats*

Amoxicillin was administered at doses of 200 mg/kg, 500 mg/kg and 1000 mg/kg orally during gestation from day 6 through 15. Amoxicillin did not modify pregnancy, percentage of resorption and did not produce fetal abnormalities as compared with negative control rats.

## Effects on Peri- and Post-Natal Development of the Rat

Amoxicillin was administered orally at 200 and 500 mg/kg/day from day 15 of gestation through lactation to 21 days post-partum. Body weight gain, pregnancy rate, and the duration of gestation of parent animals were unaffected by treatment at any dosage. There was a significant dose-related trend to lower litter size and weight at birth. This persisted through lactation to weaning despite reduced pup mortality and increased mean pup weight in the test groups compared with controls. No abnormal young were observed.

## **Special Studies**

### Acute Renal Toxicity

There was no evidence of nephrotoxicity of clarithromycin in the rat at doses up to 500 mg/kg/day.

### Hepatotoxicity

#### **BIAXIN<sup>®</sup> BID (clarithromycin tablets, USP, film-coated)**

In the *in vitro* and *in vivo* hepatotoxicity studies comparing clarithromycin with erythromycin, it was found that clarithromycin caused no greater cytotoxicity than erythromycin stearate and much less toxicity than erythromycin estolate. Hepatic enzyme induction was not found in doses below 500 mg/kg/day. In cynomolgus monkeys, the closest metabolic model for humans, elevations of ALT and LDH were identified at 200 mg/kg/day.

In dogs, a rise of ALT has been seen at 100 mg/kg/day, and in Wistar rats, a similar elevation of enzymes was seen at 200 mg/kg/day. Morphologic lesions related to prolonged exposure to clarithromycin (up to 6 months) have been consistent with reportedly reversible changes in rat, dog, and monkey studies. Such doses are many times beyond the therapeutic range in humans, which is within 8 to 10 mg/kg/day.

### Ocular Toxicity

#### **BIAXIN<sup>®</sup> BID (clarithromycin tablets, USP, film-coated)**

Ocular lesions appear confined to dogs and monkeys receiving lethal doses, which were large multiples of the human therapeutic dose. Radiolabelled clarithromycin studies indicate the eye is not selectively burdened by drug deposits and that clearance from this tissue follows that seen in other tissues. Opacities occur in the cornea following widespread extraocular tissue changes which are detectable via numerous diagnostic methods. Reduced intraocular pressure precedes corneal opacity in a relatively predictive manner. Some evidence for transient opacity and at least partial resolution was noted in animal studies, but most animals succumbed to other organ dysfunctions shortly after opacities were observed.

Animals given doses close to the therapeutic dose had no ocular changes. No ophthalmologic effects were noted in rabbits treated at doses of 40 and 160 mg/kg/day for 28 days.

### Ototoxicity

#### **BIAXIN® BID (clarithromycin tablets, USP, film-coated)**

No effects on pinna reflex were seen in guinea pigs at a dose of 400 mg/kg/day but inner and outer hair cells disappeared suggesting toxic damage. No evidence of damage was reported at 200 mg/kg/day.

### Retinal Atrophy

#### **PREVACID® (lansoprazole delayed-release capsules)**

In two 24-month toxicology studies in albino rats, drug-related retinal changes were seen at dosages of 15 mg/kg/day or higher in females and 50 mg/kg/day or higher in males. These retinal changes were similar to the spontaneous age-related and/or light induced retinal changes normally seen in rats. However, at the higher dosages, higher incidence of diffuse atrophy involving central as well as peripheral retina and a higher incidence of bilateral retinal atrophy occurred.

Retinal atrophy was only observed in albino rats treated continuously for two years. These changes in rats are believed to be associated with the effects of taurine imbalance and phototoxicity in a susceptible animal model. This lesion was not seen in other species including mice dogs and monkeys.

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## PART III: CONSUMER INFORMATION

PrHp-PAC®

**lansoprazole delayed-release capsule  
clarithromycin tablets, USP, film-coated  
amoxicillin capsules**

This leaflet is part III of a three-part "Product Monograph" published when Hp-PAC® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Hp-PAC®. Contact your doctor or pharmacist if you have any questions about the drug.

### ABOUT THIS MEDICATION

#### What the medication is used for:

The components of Hp-PAC® can be used to treat infection caused by a bacteria called *H. pylori*, and reduce the risk of duodenal ulcer recurrence. A duodenal ulcer is a sore on the lining of the duodenum, which is the beginning of the small intestine.

#### What it does:

PREVACID® (lansoprazole) helps to lower the acidity of the stomach which helps the antibiotics, BIAXIN® BID (clarithromycin) and amoxicillin, to work better to kill the bacteria in your body and helps to heal the ulcer.

#### When it should not be used:

You should not take the components of Hp-PAC® if you have an allergy to lansoprazole, clarithromycin, amoxicillin, or to any of the nonmedicinal ingredients in PREVACID®, BIAXIN® BID or amoxicillin capsules (see What the important nonmedicinal ingredients are below).

Do not take BIAXIN® BID if you are:

- sensitive to erythromycin, or other antibacterial agents of the same family;
- taking astemizole\*, cisapride\*, pimizide, terfenadine\*, ergotamine, or dihydroergotamine. These medicines can interact, possibly leading to an irregular heartbeat pattern; deaths have occurred.

\* no longer sold in Canada.

Do not take AMOXICILLIN Capsules if you have, or think you have, mononucleosis.

#### What the medicinal ingredient is:

lansoprazole; clarithromycin; amoxicillin trihydrate

#### What the important nonmedicinal ingredients are:

The nonmedicinal ingredients in PREVACID® are the following: cellulosic polymers, colloidal silicon dioxide, D & C Red No. 28, FD & C Blue No. 1, FD & C Red No. 40, gelatin, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar spheres, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide.

The nonmedicinal ingredients in BIAXIN® BID are the following: cellulosic polymers, croscarmellose sodium, D&C Yellow No. 10, magnesium stearate, povidone, propylene glycol, silicon dioxide, sorbic acid, sorbitan monooleate, stearic acid, talc, titanium dioxide and vanillin.

The nonmedicinal ingredients in the AMOXICILLIN Capsules are the following: colloidal silicon dioxide, D&C Yellow No. 10, dry-flo starch, FD&C Blue No. 1, FD&C Red No. 3, FD&C Red No. 40, FD&C Yellow No. 6, gelatin, magnesium stearate, sodium lauryl sulfate, talc and titanium dioxide.

#### What dosage forms it comes in:

The components of each daily blister pack of Hp-PAC® are as follows:

- PREVACID®: 2 x 30 mg capsules
- BIAXIN® BID: 2 x 500 mg tablets
- Amoxicillin: 4 x 500 mg capsules

Each box contains 7 daily blister packs.

### WARNINGS AND PRECAUTIONS

#### Serious Warnings and Precautions

BIAXIN® BID should not be used in pregnancy unless advised by your doctor due to potential hazards to the fetus. Do not take BIAXIN® BID without first talking to your doctor if you are breast-feeding a baby.

Serious allergic reactions (anaphylaxis), including death, have occurred in patients using penicillins (such as amoxicillin). AMOXICILLIN Capsules should not be used if you are allergic to penicillin as it may cause severe allergic reactions.

BEFORE you use Hp-PAC® talk to your doctor or pharmacist:

- about all health problems you have now or have had in the past;
- about all other medicines you are taking, including non-prescription medicines, nutritional supplements, or herbal products (see **INTERACTIONS WITH THIS MEDICATION**);
- if you have or develop severe diarrhea as this may be a sign of a more serious condition;
- if you have kidney problems;
- if you have a malignant gastric ulcer;

- if you have liver problems;
- if you are taking astemizole, terfenadine, cisapride (not currently marketed in Canada), pimoziide, ergotamine, dihydroergotamine, digoxin, or colchicine;
- if you have any unusual or allergic reaction (rash, difficulty breathing) to lansoprazole, the antibiotics clarithromycin, amoxicillin, or penicillin, any of the nonmedicinal ingredients in PREVACID<sup>®</sup>, BIAXIN<sup>®</sup> BID and AMOXICILLIN Capsules (see What the important nonmedicinal ingredients are), other medicines, foods, dyes, or preservatives.;
- if you are pregnant, trying to get pregnant or are breast-feeding.

Before taking BIAXIN<sup>®</sup> BID, tell your doctor or pharmacist:

- if you have liver or kidney disease. You may not be able to take clarithromycin. Talk to your doctor if BIAXIN<sup>®</sup> BID gives you prolonged and severe diarrhea.

The development of antibiotic resistance has been seen in patients with HIV receiving clarithromycin. To avoid failure of the treatment with a potential for developing antimicrobial resistance and a risk of failure with subsequent therapy, you should follow closely the prescribed regimen.

## INTERACTIONS WITH THIS MEDICATION

### Drugs that may interact with PREVACID<sup>®</sup> include:

- ampicillin esters
- atazanavir
- digoxin
- iron salts
- ketoconazole
- sucralfate
- theophylline
- warfarin

### Drugs that may interact with BIAXIN<sup>®</sup> BID include:

Alaprazolam, alfentanil, astemizole/terfenadine, atorvastatin, bromocriptine, carbamazepine, cilostazol, cisapride/pimoziide, colchicine, cyclosporine, digoxin, disopyramide/quinidine, ergotamine/dihydroergotamine, fluconazole, hexobarbital, lansoprazole/omeprazole, lovastatin/simvastatin, methylprednisolone, midazolam/triazolam, phenytoin, rifabutin/rifampin, ritonavir/indinavir, sildenafil, tacrolimus, theophylline, valproate, vinblastine, warfarin/acenocoumarol, zidovudine and drugs metabolized by cytochrome P450 system.

## PROPER USE OF THIS MEDICATION

### Usual Dose:

Triple Therapy: PREVACID<sup>®</sup> + BIAXIN<sup>®</sup> BID + Amoxicillin

The recommended dose is the following for 7, 10 or 14 days:

- PREVACID<sup>®</sup>: 30 mg every 12 hours
- BIAXIN<sup>®</sup> BID: 500 mg every 12 hours
- Amoxicillin: 1 g (2 x 500 mg) every 12 hours

PREVACID<sup>®</sup> should be taken prior to breakfast and another meal. You should not chew or crush PREVACID<sup>®</sup> capsules. PREVACID<sup>®</sup> capsule should be swallowed whole with sufficient water.

### Overdose:

Contact your doctor or pharmacist if you have taken more than the recommended dose. Symptoms of BIAXIN<sup>®</sup> BID overdose are abdominal pain, vomiting, nausea, and diarrhea.

### Missed Dose:

If you miss a dose, take it as soon as you can. If it is almost time for your next dose, take only that dose. Do not take double or extra doses.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, the components of Hp-PAC<sup>®</sup> can cause side effects. However, most people do not have any side effects at all.

### Hp-PAC<sup>®</sup>:

The following side effects were observed most often when all three components of Hp-PAC<sup>®</sup> were taken at the same time: abnormal taste, diarrhea, and headache. Talk to your doctor or pharmacist if any of these side effects persist or become bothersome.

### PREVACID<sup>®</sup>:

The following side effects have been reported (occurring between 1% and 10% in clinical trials): arthralgia (muscle pain), belching, constipation, diarrhea, dizziness, dry mouth, gas, headache, indigestion, insomnia, nausea, rash, vomiting, weakness. Talk to your doctor or pharmacist if any of these side effects persist or become bothersome.

If the following symptoms appear, consult your physician: bladder infection (pain, burning sensation upon urination) and upper respiratory tract infections (e.g., bronchitis, sinusitis, runny nose, sore throat).

Serious side effects from lansoprazole are not common.

### BIAXIN<sup>®</sup> BID:

Like all medicines, BIAXIN<sup>®</sup> BID can cause side effects. The majority of side effects observed in clinical trials with BIAXIN<sup>®</sup> BID were of a mild and transient nature.

The following adverse reactions were reported during the clinical studies with clarithromycin, the medicinal ingredient (occurring between 1% and 10% in clinical trials) or during post-marketing surveillance: abdominal pain, abnormal taste, diarrhea, ear disorder, flatulence, indigestion, headache, nausea, rash, vomiting. Talk to your doctor or pharmacist if any of these side effects persist or become bothersome.

Serious side effects from BIAXIN® BID are not common.

**AMOXICILLIN:**

Like all medicines, amoxicillin can cause side effects. The following side effects have been reported: diarrhea, nausea, rash and vomiting. Talk to your doctor or pharmacist if any of these side effects persist or become bothersome.

<b>SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM</b>				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
<b>Hp-PAC®</b>				
<b>Uncommon</b>	Severe diarrhea			✓
<b>PREVACID®</b>				
<b>Uncommon</b> (occurring between 0.2% and 1% in clinical trials)	Abdominal pain		✓	
	Severe diarrhea accompanied with blood and/or mucous			✓
<b>BIAXIN® BID</b>				
<b>Uncommon</b>	Allergic reactions*			✓
	Severe diarrhea		✓	
	Severe abdominal cramps		✓	
	Irregular heart beat			✓
<b>AMOXICILLIN</b>				
<b>Uncommon</b>	Allergic reactions*			✓

\*Allergic reactions, with symptoms such as itching, skin eruptions, rash, sore throat, fever, swelling, skin rash, itchiness, difficulty breathing, lightheadedness/dizziness.

*This is not a complete list of side effects. For any unexpected effects while taking Hp-PAC®, contact your doctor or pharmacist.*

**HOW TO STORE IT**

Keep Hp-PAC® and all other medicines out of reach of children.

Store at room temperature (15 - 25°C / 59 - 77°F) in the original package. Protect from light and moisture. Do not use beyond the expiration date.

**REPORTING SUSPECTED SIDE EFFECTS**

**To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:**

**Toll-free telephone: 1-866-234-2345**  
**Toll-free fax: 1-866-678-6789**  
**By email: [cadrmpp@hc-sc.gc.ca](mailto:cadrmpp@hc-sc.gc.ca)**

**By regular mail:**  
**National AR Centre**  
**Marketed Health Products Safety and Effectiveness**  
**Information Division**  
**Marketed Health Products Directorate**  
**Tunney's Pasture, AL 0701C**  
**Ottawa ON K1A 0K9**

*NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.*

**MORE INFORMATION**

This document plus the full Product Monograph, prepared for health professionals can be found at: <http://www.abbott.com> or by contacting the sponsor, Abbott Laboratories, Limited, Saint-Laurent, Qc H4S 1Z1 at: 1-800-699-9948

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