

New Drug

Dexlansoprazole: A Proton Pump Inhibitor With a Dual Delayed-Release System

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ABSTRACT

Background: Dexlansoprazole, the dextrorotatory enantiomer of lansoprazole, is a proton pump inhibitor (PPI) formulated to have dual delayed-release properties. It is indicated for healing all grades of esophagitis, maintaining the healing of erosive esophagitis (EE), and treating heartburn associated with nonerosive gastroesophageal reflux disease.

Objective: This article reviews the pharmacology, pharmacokinetics, and pharmacodynamics of dexlansoprazole, as well as its clinical efficacy and tolerability.

Methods: MEDLINE (1966–April 2010) and International Pharmaceutical Abstracts (1970–April 2010) were searched for original research and review articles published in English using the terms *dexlansoprazole* and *TAK-390MR*. The reference lists of identified articles were reviewed for additional pertinent publications. Abstracts from 2007–2009 American College of Gastroenterology and Digestive Disease Week meetings were searched using the same terms.

Results: By irreversibly binding to H⁺K⁺-ATPase, dexlansoprazole inhibits acid production by the parietal cell. Its dual delayed-release formulation provides 2 distinct releases of medication, prolonging the mean residence time compared with lansoprazole (5.56–6.43 vs 2.83–3.23 hours, respectively). In 2 identical Phase III trials of the healing of EE, there were no significant differences in rates of complete healing after 8 weeks between dexlansoprazole 60 and 90 mg once daily and lansoprazole 30 mg once daily. In 2 studies of the maintenance of healing of EE, rates of healing at 6 months were significantly higher with dexlansoprazole 30, 60, and 90 mg once daily compared with placebo ($P < 0.001$). Patients with nonerosive reflux disease who received dexlansoprazole 30 or 60 mg once daily had significantly more 24-hour heartburn-free days com-

pared with those who received placebo ($P < 0.001$). Dexlansoprazole was well tolerated compared with placebo or lansoprazole in all studies.

Conclusions: In the studies reviewed, dexlansoprazole was well tolerated and effective in the healing and maintenance of EE, and in the treatment of nonerosive reflux disease. However, most of the available evidence involved comparisons with placebo, making it difficult to draw meaningful conclusions about the place of dexlansoprazole among PPIs. More head-to-head comparative trials with other PPIs are needed to determine whether the unique formulation of dexlansoprazole translates into a clinically meaningful improvement in outcomes. (*Clin Ther.* 2010;32:1578–1596) © 2010 Excerpta Medica Inc.

Key words: dexlansoprazole, TAK-390MR, proton pump inhibitors, esophagitis, gastroesophageal reflux.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is the abnormal reflux of gastric contents into the esophagus, leading to symptoms or esophageal damage.^{1,2} Esophageal symptoms of GERD include persistent heartburn, belching, hoarseness, sore throat, and changes in the voice. Extraesophageal symptoms may include cough, wheezing, shortness of breath, early satiety, hiccups, and noncardiac chest pain. GERD is further categorized as nonerosive reflux disease (NERD) and more advanced manifestations that include erosive esophagitis (EE) and Barrett's esophagus.

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It has been estimated that 15% to 20% of the US population experience symptoms of GERD at least weekly, with an incidence of <5% in Asian countries and from 5% to 15% in European countries.³ NERD accounts for ~70% of patients with GERD, EE for ~25%, and Barrett's esophagus for ~5%.⁴ If GERD is untreated or inadequately treated, the condition may predispose patients to such serious complications as erosions, strictures, Barrett's esophagus, and adenocarcinoma.⁵⁻⁹

Due to improved symptom relief and healing with proton pump inhibitors (PPIs) compared with histamine-2 receptor antagonists (H₂RAs) and antacids, guidelines for the diagnosis and treatment of GERD from the American College of Gastroenterology recommend the use of PPIs over H₂RAs or antacids in patients with EE.^{1,2} Long-term, possibly lifelong, PPI treatment is usually required, as symptoms may recur after discontinuation of therapy.

Patients with NERD are managed based on the severity of their symptoms. For mild intermittent symptoms, lifestyle modification and antacids with/without an H₂RA or PPI are routinely recommended.¹ When symptoms are more severe or more frequent, a PPI is recommended for improved symptom control. Patients who fail to respond to therapy should be referred for further diagnostic testing. In most efficacy studies, the initial course of PPI treatment in patients with NERD has been 4 weeks⁴; however, there is evidence suggesting that longer courses of treatment may provide added benefit.¹⁰ If symptoms relapse after a course of treatment, patients should be placed on a therapeutic regimen that controls their symptoms and prevents complications. Some strategies for improving symptom control include increasing the dose or the frequency of PPI administration.¹

It has been estimated that ~10% of patients with EE do not achieve healing after 8 weeks of PPI therapy, and ~40% of patients with NERD do not have a sustained symptomatic response after 4 weeks of PPI therapy.^{4,11,12} In studies of EE healing, patients with more severe EE (Los Angeles [LA] grades C and D) have been less responsive to PPI therapy compared with those with less severe EE (LA grades A and B). For example, in a randomized, double-blind, parallel-group study, Castell et al¹³ compared EE healing rates in patients receiving esomeprazole 40 mg once daily (n = 2624) or lansoprazole 30 mg once daily (n = 2617) for 8 weeks. At 8 weeks, overall healing rates using the life-table analysis were 92.6% in the esomeprazole group and

88.8% in the lansoprazole group ($P < 0.001$). In another randomized, double-blind, parallel-group study, Richter et al¹⁴ determined EE healing rates after 8 weeks of treatment with esomeprazole 40 mg once daily (n = 1216) or omeprazole 20 mg once daily (n = 1209). Using the life-table analysis, overall EE healing rates were 93.7% in patients who received esomeprazole and 84.2% in those who received omeprazole ($P < 0.001$).

Fennerty et al¹⁵ conducted an 8-week, randomized, double-blind, parallel-group study of esomeprazole 40 mg once daily (n = 488) or lansoprazole 30 mg once daily (n = 501) in patients with moderate to severe EE (LA grades C and D). Healing rates with esomeprazole at 8 weeks, using the life-table analysis, were 80.3% in patients with LA grade C disease at baseline and 67.6% in those with LA grade D disease at baseline. In the lansoprazole group, the corresponding healing rates were 74.9% and 66.3%. In a multicenter, randomized, double-blind study in patients with all grades of EE, Labenz et al¹⁶ compared healing rates with esomeprazole 40 mg once daily (n = 1562) and pantoprazole 40 mg once daily (n = 1589). Using the life-table analysis, healing rates at 8 weeks for patients in the esomeprazole group with LA grades A, B, C, and D were 97.3%, 96.9%, 91.3%, and 88.1%, respectively. The corresponding rates in the pantoprazole group were 97.1%, 93.1%, 87.6%, and 73.6%.

Some proposed theories for the lack of sustained response to PPIs include extraesophageal disease involvement, poor compliance, PPI resistance, visceral hypersensitivity, genetic variation, nocturnal acid breakthrough, inappropriate timing of PPI dosing relative to meals, and pharmacokinetic limitations of delayed-release PPIs.^{4,11,12} The pharmacokinetic limitations of PPIs stem from their short $t_{1/2}$ s and the physiology of the parietal cell and proton pumps. At any given time, only 70% to 80% of proton pumps are active within the parietal cell.¹¹ Therefore, when PPIs are given once daily, they irreversibly bind to H⁺K⁺-ATPase and maximally inhibit 70% to 80% of proton pumps. However, because of the short elimination $t_{1/2}$ s (≤ 2 hours) of rabeprazole, esomeprazole, omeprazole, pantoprazole, and lansoprazole,¹⁷⁻²¹ active drug is no longer present when proton pumps regenerate.

Dexlansoprazole* is the newest addition to the PPI class in the United States, approved by the US Food and

*Trademark: Dexilent® (Takeda Pharmaceuticals North America, Inc., Deerfield, Illinois).

Drug Administration in January 2009 for the healing of all grades of esophagitis, maintenance of the healing of EE, and treatment of heartburn associated with NERD.²² It is formulated with dual delayed-release technology to provide 2 distinct releases of medication.

This article reviews the pharmacology, pharmacokinetics, pharmacodynamics, clinical efficacy, tolerability, and cost of dexlansoprazole in adult patients with EE and NERD.

METHODS

MEDLINE (1966–April 2010) and International Pharmaceutical Abstracts (1970–April 2010) were searched for original research and review articles published in English using the terms *dexlansoprazole* and *TAK-390MR*. Articles relating to the pharmacology, pharmacokinetics, pharmacodynamics, clinical efficacy, and tolerability of dexlansoprazole were analyzed for inclusion in the review. The reference lists of identified articles were reviewed for additional pertinent publications. Abstracts from 2007–2009 American College of Gastroenterology and Digestive Disease Week meetings were searched using the same terms.

CLINICAL PHARMACOLOGY

Dexlansoprazole is chemically described as (+)-2-[(R)-[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulfinyl]-1H-benzimidazole. It has a molecular weight of 369.36 and an empiric formula of $C_{16}H_{14}F_3N_3O_2S$. Dexlansoprazole is the dextrorotatory enantiomer of lansoprazole (also expressed as *R*-lansoprazole or [+]-lansoprazole). Its chemical structure is illustrated in the figure.

In animals administered lansoprazole 50 mg/kg, the AUC and C_{max} of (+)-lansoprazole were significantly increased compared with those of (–)-lansoprazole ($P < 0.05$).^{23,24} Studies in humans have reported a reduction in clearance and increase in terminal elimination $t_{1/2}$ for the (+)-enantiomer of lansoprazole (dexlansoprazole) compared with the (–)-enantiomer, resulting in higher and more prolonged serum concentrations.²⁵

Mechanism of Action

Dexlansoprazole selectively suppresses gastric acid secretion by direct inhibition of the H^+K^+ -ATPase proton pump in the gastric parietal cell. Inhibition of this cell membrane enzyme ultimately blocks the final step in acid production.²²

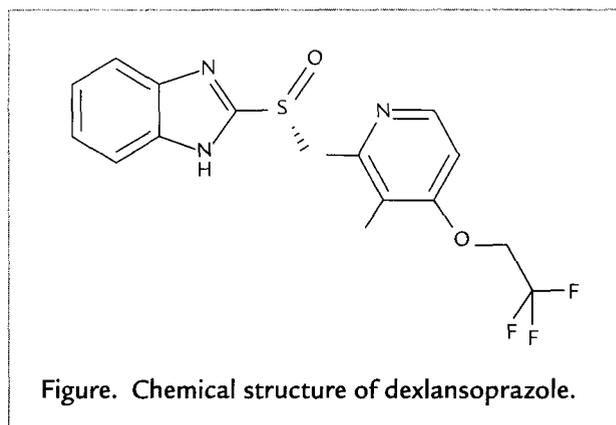


Figure. Chemical structure of dexlansoprazole.

Pharmacokinetics

Unlike the other PPIs available in the United States (omeprazole, esomeprazole, rabeprazole, pantoprazole, and lansoprazole), which provide a single release of medication, dexlansoprazole is formulated with a unique dual delayed-release technology. The formulation incorporates 2 types of enteric-coated granules that are soluble at different physiologic pH values. Dexlansoprazole is initially released in the proximal small intestine, typically 1 to 2 hours after administration, when the gastric pH reaches ~5.5. A second release of medication occurs several hours later in the distal region of the small intestine, when the gastric pH reaches ~6.75.^{11,25,26}

Vakily et al²⁵ conducted 2 Phase I, randomized, open-label, multiple-dose crossover studies evaluating the pharmacokinetics and pharmacodynamics of dexlansoprazole in healthy male and female volunteers aged 18 to 55 years with a body mass index of 18 to 30 kg/m². In the first study ($n = 40$), dexlansoprazole 60, 90, and 120 mg and lansoprazole 30 mg were each administered orally once daily for 5 days. In the second study ($n = 45$), dexlansoprazole 30 and 60 mg and lansoprazole 15 mg were each administered once daily for 5 days. Lansoprazole dosing in these studies was consistent with the standard doses for various acid-related disorders. In both studies, drugs were given at ~9 AM after a fast of at least 10 hours. On each study day, participants received a standard breakfast 1 hour after dosing, lunch 4 hours after dosing, dinner 9 hours after dosing, and a snack 12 hours after dosing. Treatments were separated by a washout period of at least 5 days. In both studies, the mean C_{max} and AUC of dexlansoprazole after single and multiple daily doses increased in a dose-proportional manner (Table I). The AUC was ~3, 5, and 7 times higher with dexlansoprazole 60, 90, and

Table 1. Comparison of selected pharmacokinetic estimates for dexlansoprazole and lansoprazole in the 2 randomized, open-label, multiple-dose crossover studies by Vakily et al.²⁵ Values are mean (SD).

Study/Drug	C_{max} , ng/mL		AUC_{0-t} , ng · h/mL	
	Day 1	Day 5	Day 1	Day 5
Study 1 (N = 40)				
Dexlansoprazole 60 mg	1290 (735)	1434 (703)	5995 (4436)	6373 (4780)
Dexlansoprazole 90 mg	1775 (959)	2197 (923)	8564 (6337)	9751 (6728)
Dexlansoprazole 120 mg	2428 (1020)	2517 (1158)	12,447 (9335)	13,220 (9386)
Lansoprazole 30 mg	840 (336)	845 (380)	2041 (1674)	1886 (1547)
Study 2 (N = 45)				
Dexlansoprazole 30 mg	576 (311)	658 (263)	2893 (1475)	3182 (1559)
Dexlansoprazole 60 mg	1208 (556)	1388 (736)	5885 (2707)	6463 (3102)
Lansoprazole 15 mg	424 (157)	402 (157)	1049 (504)	1046 (502)

120 mg, respectively, compared with lansoprazole. C_{max} was ~1.5, 2.5, and 3 times higher with dexlansoprazole 60, 90, and 120 mg compared with lansoprazole 30 mg.

Absorption

Lee et al²⁷ conducted a single-dose, open-label, 4-way crossover study of the effect and timing of food on the pharmacokinetics of dexlansoprazole in 48 healthy male and female volunteers. All subjects received placebo on day 1, after which they received dexlansoprazole 90 mg on day 3 under each of the following conditions, in randomized sequence: in the fasted state; 5 minutes before a standard high-fat breakfast; 30 minutes before the high-fat breakfast; and 30 minutes after the start of the high-fat breakfast. There was a washout period of ≥ 5 days between each of the 4 fed states. All subjects also received a standard lunch, dinner, and snack on days 1 and 3. Although all 48 subjects were included in the final safety analysis, only 46 were randomized to the 4 sequence groups (1 withdrew consent and 1 withdrew due to an adverse event). After administration of dexlansoprazole in the fed and fasted states, 2 distinct peaks were observed in the dexlansoprazole plasma concentration–time curve. The mean C_{max} was 1825 ng/mL when dexlansoprazole was administered 30 minutes after the high-fat breakfast, compared with 1486 ng/mL when it was administered in the fasted state. The corresponding values for mean AUC were 7999 and 6996 ng · h/mL, respectively. Based on these results, it appears that dexlansoprazole can be taken without regard to meals.

In a Phase I, open-label, 2-way crossover study, Czerniak et al²⁸ studied the bioequivalence of dexlansoprazole administered as granules sprinkled over 1 tablespoon of applesauce and as an intact capsule taken with 240 mL of water in 50 healthy volunteers. Bioequivalence was determined by ANOVA using the point estimates and 90% CIs for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$, which were 0.94 (90% CI, 0.870–1.023), 0.95 (90% CI, 0.894–1.000), and 0.94 (90% CI, 0.890–0.995), respectively. All 90% CIs were within the bioequivalence range of 0.8–1.25. Therefore, sprinkling dexlansoprazole granules over applesauce appears to be an option for patients who are unable to swallow the whole capsule.

Distribution

Plasma protein binding of dexlansoprazole in healthy subjects has been reported to range from 96.1% to 98.8%, independent of plasma concentrations.²² After administration of several doses of dexlansoprazole in patients with symptomatic GERD, the apparent V_d was 40.3 L.

Metabolism

Grabowski et al²⁹ evaluated the metabolism of dexlansoprazole in 6 healthy male subjects. Subjects received 60 mg of nonradiolabeled dexlansoprazole orally once daily for 4 days and a single oral dose of 60 mg [¹⁴C]-dexlansoprazole suspension with aluminum hydroxide 200 mg/magnesium hydroxide 200 mg/simethicone 20 mg suspension on day 5. Plasma, urine, and feces were collected and analyzed for 7 days. Dexlansoprazole

was metabolized in the liver by oxidation and reduction to inactive metabolites. Oxidative metabolites are formed by the cytochrome P450 (CYP) system, specifically through hydroxylation via CYP2C19 and oxidation to the sulfone via CYP3A4.

Elimination

Grabowski et al²⁹ also evaluated the elimination of dexlansoprazole after administration of [¹⁴C]-dexlansoprazole in the same 6 healthy male subjects. The mean (SD) amounts recovered in the urine and feces were 50.7% (9.0%) and 47.6% (7.3%), respectively. The parent compound was not detected in the urine, although 6 inactive metabolites were identified with a mean of 85% urinary radioactivity. The 4 major inactive metabolites recovered in the urine were 5-glucuronyloxy dexlansoprazole, 5-glucuronyloxy dexlansoprazole sulfide, 2-*S-N*-acetylcysteinyl benzimidazole, and 5-sulfonyloxy dexlansoprazole sulfide. Six inactive metabolites and parent drug were recovered in the feces, accounting for a mean 72% of fecal radioactivity.

Special Populations

Renal Impairment

The prescribing information for dexlansoprazole recommends no dose adjustment in patients with renal impairment.²² However, the literature search identified no studies conducted in patients with documented renal impairment. Thus, dexlansoprazole should be used with caution in patients with renal impairment.

Hepatic Impairment

Lee et al³⁰ investigated the effects of a single dose of dexlansoprazole 60 mg in 12 subjects with moderate hepatic impairment (Child-Pugh class B) and 12 healthy volunteers. The mean (SD) AUC of dexlansoprazole was significantly increased in subjects with hepatic impairment compared with healthy volunteers (16,306 [9209] vs 7563 [9794] ng · h/mL, respectively; $P < 0.01$). The mean unbound C_{max} was also significantly higher in patients with hepatic impairment (27.3 [12.2] vs 17.9 [9.1] ng/mL; $P \leq 0.05$). A higher unbound C_{max} results in more free drug circulating in the plasma, which may increase the pharmacologic effects of dexlansoprazole. The authors did not consider the observed differences clinically relevant and did not suggest dose adjustment in patients with mild or moderate hepatic impairment (Child-Pugh class A and B, respectively). However, the prescribing information for dexlansoprazole recommends

a maximum dose of 30 mg once daily for patients with moderate hepatic impairment.²² The literature search identified no studies of dexlansoprazole in patients with severe hepatic impairment (Child-Pugh class C).

Pediatric Population

Because there have been no studies of the safety profile and efficacy of dexlansoprazole in the pediatric population, use of dexlansoprazole is not recommended in these patients.²²

Pregnancy and Lactation

There have been no adequate, well-controlled studies of dexlansoprazole in pregnant or lactating women. Dexlansoprazole is classified as pregnancy category B, indicating that there is no evidence of fetal risk in humans. To make this determination, data indicating no fetal risk were extrapolated from animal-reproduction studies and are not entirely applicable to human subjects. Until further data become available, it is advisable to avoid dexlansoprazole during pregnancy and lactation unless there is a significant need.²²

Age and Sex

Vakily et al³¹ conducted a Phase I, open-label, parallel-group study to compare the effects of sex and age on the pharmacokinetics of dexlansoprazole. The study enrolled 12 men and 12 women who were in good health and were aged between 18 and 40 years (young; $n = 12$) and 65 and 80 years (elderly; $n = 12$). Participants received a single oral dose of dexlansoprazole 60 mg, and blood samples were obtained for determination of plasma concentrations and calculation of pharmacokinetic parameters before and after dosing. The $AUC_{0-\infty}$ was 42.8% higher in women than in men (10,685 and 7483 h · ng/mL, respectively; P value not reported). The terminal $t_{1/2}$ was significantly longer in elderly subjects compared with younger subjects (2.23 vs 1.5 hours, respectively; $P \leq 0.05$). The authors considered these differences clinically irrelevant. The prescribing information for dexlansoprazole recommends no dose adjustment based on sex or age.²²

Genetic Polymorphisms

In Japanese male subjects who received a single dose of dexlansoprazole 30 or 60 mg (2–6 subjects per group), the pharmacokinetics of dexlansoprazole were reported to be considerably affected by CYP2C19 polymorphisms.²² Mean C_{max} and AUC were found to be 2 times

higher in intermediate metabolizers compared with extensive metabolizers. Mean C_{\max} and AUC were 4 and 12 times higher, respectively, in poor metabolizers compared with extensive metabolizers. Although the study included no white or black subjects, dexlansoprazole exposure would also be expected to be affected by CYP2C19 polymorphisms in these groups.

Drug-Drug Interactions

Because of dexlansoprazole's extensive hepatic metabolism via CYP3A4 and CYP2C19^{22,29,32} and its alteration of the gastric pH, drug-drug interactions are a clinically relevant concern when prescribing dexlansoprazole. Vakily et al³² assessed the effect of dexlansoprazole on the pharmacokinetics of diazepam, phenytoin, warfarin, and theophylline in 4 separate single-center, randomized, double-blind, placebo-controlled, 2-way crossover studies in healthy volunteers.

In the first of these studies, 20 healthy subjects were randomized to receive 9 to 11 daily doses of dexlansoprazole 90 mg along with a single oral dose of diazepam 5 mg on day 6 or 8, or placebo along with a single oral dose of diazepam 5 mg on day 6 or 8, in a 2-way crossover fashion.³² When subjects received dexlansoprazole and diazepam, the mean (SD) elimination $t_{1/2}$ of diazepam was 61.18 (33.41) hours, compared with 51.49 (19.67) hours with placebo and diazepam. The diazepam AUC_{0-t} was 3473.56 (936.74) ng · h/mL when subjects received dexlansoprazole and diazepam, compared with 3388.61 (863.54) ng · h/mL with placebo and diazepam. The authors reported that the 90% CIs for the ratios of the central values fell within the bioequivalence range of 0.8–1.25, although supporting data were not provided.

In the second study, 16 healthy subjects were randomized to receive 9 to 11 daily doses of dexlansoprazole 90 mg along with a single oral dose of phenytoin 250 mg on day 6 or 8, or placebo along with a single oral dose of phenytoin 250 mg on day 6 or 8, in a 2-way crossover fashion.³² When subjects received dexlansoprazole and phenytoin, the elimination $t_{1/2}$ of phenytoin was 13.55 (2.46) hours, compared with 13.65 (2.92) hours with placebo and phenytoin. The AUC_{0-t} of phenytoin was 111.90 (27.04) ng · h/mL when subjects received dexlansoprazole and phenytoin, compared with 113.41 (26.18) ng · h/mL with placebo and phenytoin. The authors again stated that the 90% CIs for the ratios of the central values fell within the bioequivalence range of 0.8 to 1.25, although supporting data were not provided.

In the third study, 19 healthy subjects were randomized to receive 9 to 11 daily doses of dexlansoprazole 90 mg along with a single oral dose of warfarin 25 mg on day 6 or 8, or placebo along with a single oral dose of warfarin 25 mg on day 6 or 8, in a 2-way crossover fashion.³² When subjects received dexlansoprazole and warfarin, the elimination $t_{1/2}$ of *S*-warfarin was 42 (9) hours, compared with 40 (7) hours with placebo and warfarin. The elimination $t_{1/2}$ of *R*-warfarin was 49 (11) hours when subjects received dexlansoprazole and warfarin and when they received placebo and warfarin. When subjects received dexlansoprazole and warfarin, the AUC_{0-t} for *S*-warfarin was 50,110 (11,381) ng · h/mL, compared with 47,920 (10,096) ng · h/mL with placebo and warfarin. The AUC_{0-t} for *R*-warfarin was 73,030 (10,481) ng · h/mL when subjects received dexlansoprazole and warfarin, compared with 71,050 (10,166) ng · h/mL when they received placebo and warfarin. The authors reported that the 90% CIs for the ratios of the central values fell within the bioequivalence range of 0.8 to 1.25, but no supporting data were provided. Although these data suggest no drug-drug interaction between dexlansoprazole and warfarin, the prescribing information for dexlansoprazole recommends monitoring for increases in the international normalized ratio and prothrombin time.²²

In the final study, 20 healthy subjects were randomized to receive 9 to 11 daily doses of dexlansoprazole 90 mg along with a single intravenous dose of aminophylline 400 mg (equivalent to theophylline 315 mg) on day 6 or 8, or placebo along with a single intravenous dose of aminophylline 400 mg on day 6 or 8, in a 2-way crossover fashion.³² When subjects received dexlansoprazole and aminophylline, the elimination $t_{1/2}$ of theophylline was 8.48 (1.6) hours, compared with 9.26 (1.8) hours with placebo and aminophylline. The mean AUC_{0-t} of theophylline was 122,300 (28,680) ng · h/mL when subjects received dexlansoprazole and aminophylline, compared with 126,600 (28,430) ng · h/mL with placebo and phenytoin. Once more, the 90% CIs for the ratios of the central values were reported to fall within the bioequivalence range of 0.8 to 1.25, although no data were provided.

Based on the results of these single-dose pharmacokinetic analyses, dose adjustments appear to be unnecessary when dexlansoprazole is administered concomitantly with diazepam, phenytoin, warfarin, or theophylline. However, the pharmacokinetic effect of prolonged concomitant administration of these agents

may be different from the effects observed with single-dose administration. Further pharmacokinetic studies are needed to fully elucidate the effects of prolonged coadministration of dexlansoprazole with these and other medications.

Although no pertinent studies were identified in the literature search, the prescribing information for dexlansoprazole discusses the potential for drug–drug interactions with medications that have pH-dependent absorption, recommending against concomitant administration of dexlansoprazole with atazanavir.²² Digoxin, iron salts, azole antifungals, and ampicillin esters also have pH-dependent absorption and their pharmacokinetics may be altered by concomitant administration of dexlansoprazole, although no pertinent studies were identified in the literature search. Given the metabolism of dexlansoprazole via the CYP3A4 isozyme,²⁹ potent CYP3A4 inhibitors may theoretically alter the metabolism of dexlansoprazole, leading to higher concentrations of the active parent compound.

The potential for drug–drug interaction between clopidogrel and CYP2C19 inhibitors such as dexlansoprazole is not mentioned in the prescribing information for dexlansoprazole. Clopidogrel is a prodrug that when active, inhibits platelet aggregation by selectively and irreversibly inhibiting the binding of adenosine diphosphate (ADP) to its platelet receptor, which in turn inhibits activation of the ADP-mediated glycoprotein IIb/IIIa complex. The activation of clopidogrel occurs primarily through CYP2C19. By inhibiting CYP2C19, dexlansoprazole could potentially inhibit the activation of clopidogrel. The implications of this interaction are not well understood, and there are conflicting reports in the literature for the other available PPIs.^{33–36} At this time, the prescribing information for clopidogrel recommends avoiding the combination of clopidogrel and agents that inhibit CYP2C19, unless clinically necessary.³⁷

Pharmacodynamics

Wu et al²⁶ conducted a retrospective post hoc analysis of data from 3 Phase I, single-center, open-label, multiple-dose crossover studies. Because the mucosa has decreased ability to heal when the gastric pH is not maintained at >4, the goals of the analysis were to determine the threshold plasma concentration that was best correlated with a pH >4, to identify a model that maximized the relationship between the percent of time the intragastric pH is >4 and the percent of time plasma concentrations

are above the threshold over the 24-hour period after dosing, and to use this percent of time above the threshold to estimate the percent of time pH is maintained at >4. Based on data from patients receiving dexlansoprazole and lansoprazole, the threshold plasma concentration was identified as 125 ng/mL. The mean percent of time plasma concentrations were above this threshold was 17% for lansoprazole 30 mg, compared with 34% to 50% for dexlansoprazole doses of 30 to 120 mg. The mean percent of time above the threshold for lansoprazole corresponded to an estimated 50% of time with a pH >4, compared with 65% to 70% for the various dexlansoprazole regimens. No statistical analysis was provided. Based on these results, dexlansoprazole appeared to maintain plasma drug concentrations above the threshold of 125 ng/mL for at least 2 times longer than lansoprazole, producing a greater percent of time with a pH >4.

After 5 days of treatment in the Phase I pharmacokinetic/pharmacodynamic studies by Vakily et al²⁵ described earlier, the mean intragastric pH was >4 for 59.2% and 66.7% of a 24-hour period in subjects receiving dexlansoprazole 30 and 90 mg, respectively. In addition, the mean residence time (the time a drug molecule spends in the systemic circulation) ranged from 5.56 to 6.34 hours for the various dexlansoprazole doses, compared with 2.83 to 3.23 hours for lansoprazole.

In the 4-way crossover study by Lee et al²⁷ discussed earlier, placebo administration on day 1 and drug administration on day 3 were followed by 24 hours of ambulatory continuous intragastric pH monitoring. On day 3, the percent of time that intragastric pH was >4 after administration of a single dose of dexlansoprazole 90 mg in the fasted state, 30 minutes before breakfast, 5 minutes before breakfast, and 30 minutes after breakfast were 64%, 66%, 62%, and 57%, respectively. When patients received dexlansoprazole 90 mg 30 minutes after the start of breakfast, the percent of time intragastric pH was >4 was significantly shorter compared with administration in the fasted state (64% vs 57%, respectively; $P < 0.05$). On day 3, the mean intragastric pH over 24 hours after administration of a single dose of dexlansoprazole 90 mg in the fasted state, 30 minutes before breakfast, 5 minutes before breakfast, and 30 minutes after breakfast was 4.46, 4.53, 4.43, and 4.25, respectively. None of the differences between the fed and fasted states reached statistical significance. Based on the results of this study, administration of dexlansoprazole without regard to meals is

unlikely to have a clinically relevant effect on efficacy. However, it should be noted that this study was conducted in healthy subjects, had a small sample size, and examined the effects of only a single dose of dexlansoprazole. Different patients may have different responses to dexlansoprazole, and it seems reasonable to suggest taking the medication before meals if a patient is not responding to dexlansoprazole taken with food.

Zhang et al^{38,39} conducted a randomized, open-label, 3-period crossover study of the effects of dexlansoprazole on plasma gastrin concentrations in 42 healthy subjects aged 18 to 55 years. Subjects received dexlansoprazole 90 mg, dexlansoprazole 120 mg, and lansoprazole 30 mg once daily (14 in each group) for 5 days each, with a washout period of at least 14 days between regimens. Gastrin concentrations appeared comparable in the dexlansoprazole 90- and 120-mg groups on days 5 and 6 (Table II). The explanation for the lack of difference remains to be determined, although it could have been the result of a ceiling or saturation effect with escalating doses of dexlansoprazole. Gastrin concentrations returned to baseline within 1 week after discontinuation of dexlansoprazole. Scatter plots of plasma gastrin AUC₀₋₂₄ indicated no dose-response relationship between regimens. Mild adverse events included upper respiratory tract symptoms (n = 14 patients), headache (n = 12), nasal congestion and inflammation (n = 7), nausea and vomiting (n = 7), and diarrhea/gastrointestinal symptoms (n = 6). No serious adverse events or deaths were reported.

Vakily et al⁴⁰ conducted a single-center, single-dose, randomized, active- and placebo-controlled, 4-period crossover study of the electrocardiographic effects of dexlansoprazole. Participants were randomly assigned

in 1:1:1:1 ratio to the sequence in which they would receive 4 oral regimens: blinded dexlansoprazole 90 mg, blinded dexlansoprazole 300 mg, blinded placebo, and open-label moxifloxacin 400 mg. Regimens were separated by a washout period of 5 days. ECG recordings were obtained by 24-hour, 12-lead Holter monitoring on day -1 (baseline) and on day 1 of each dosing period, starting 30 minutes before the dose. As expected, moxifloxacin was associated with significant prolongation of the Fridericia-corrected QT (QTc) interval compared with placebo ($P < 0.001$) (Table III). The authors reported no significant differences between the dexlansoprazole groups and placebo, although P values were not provided.

CLINICAL EFFICACY AND TOLERABILITY

Healing of Erosive Esophagitis

Sharma et al⁴¹ conducted 2 identically designed multinational, randomized, double-blind, active-controlled Phase III studies comparing dexlansoprazole and lansoprazole in the treatment of EE. Patients aged ≥ 18 years with endoscopically confirmed EE at screening were randomized to receive dexlansoprazole 60 mg once daily (study 1, n = 680; study 2, n = 694), dexlansoprazole 90 mg once daily (n = 668 and n = 687, respectively), or lansoprazole 30 mg once daily (n = 690 and n = 673) for 8 weeks. The lansoprazole dose used in this study is the approved dose for the short-term treatment of EE.²¹ Patients were excluded if they tested positive for *Helicobacter pylori*, required prescription or nonprescription PPIs or H₂RAs at screening and during the study, used NSAIDs chronically (>12 doses per month), had a coexisting disease that affected the esophagus, had a history of active gastric or duodenal ulcers within

Table II. Changes from baseline in gastrin concentrations after 5 days of dosing with dexlansoprazole and lansoprazole in the randomized, open-label, 3-period crossover study by Zhang et al.³⁹ Values are mean (SD).

Drug/Dose	Gastrin, pg/mL		
	Baseline	Day 5	Day 6
Dexlansoprazole 90 mg	18 (5.8)	68 (47.9)*	83 (66.2)*
Dexlansoprazole 120 mg	20 (11.1)	67 (53.2)*	91 (72.9)*
Lansoprazole 30 mg	20 (12.6)	45 (33.1)*	57 (46.7)*

* $P < 0.05$ versus baseline.

Table III. Changes in Fridericia-corrected QT (QTc) interval after administration of placebo, moxifloxacin, and dexlansoprazole in the randomized study by Vakily et al.⁴⁰

Study Arm	Maximum QTc Interval, Mean (SD), msec	Time-Averaged QTc Interval, Mean (SD), msec
Placebo	408.2 (16.29)	391.8 (14.65)
Moxifloxacin 400 mg	416.5 (19.74)*	399.6 (17.78)*
Dexlansoprazole 90 mg	409.9 (18.28)	394.3 (15.36)
Dexlansoprazole 300 mg	409.3 (17.51)	392.1 (15.59)

* $P < 0.001$ versus placebo.

4 weeks of the first dose of study drug, or had acute upper gastrointestinal hemorrhage within 4 weeks of screening. Pregnant or lactating women were also excluded. Patients were stratified by disease severity (LA classification) at the initial screening visit.

The 2 studies included a total of 4092 randomized patients.⁴¹ The demographic characteristics of patients in the 2 studies were well matched at baseline, with no significant differences between groups. The proportions of randomized patients in the various LA classes at baseline in the 2 studies are summarized in Table IV. Healing rates in the dexlansoprazole 60- and 90-mg groups met the prespecified criterion for noninferiority in both studies and were tested for superiority to lansoprazole. Using the crude rate analysis, the absolute differences in EE healing at week 8 between dexlansoprazole 90 mg and lansoprazole 30 mg in studies 1 and 2 were 6.8% and 4.8%, respectively (both, $P < 0.05$) (Table V). The clinical relevance of these small absolute differences remains to be determined. In patients receiving dexlansoprazole 60 mg, the absolute differences in EE healing compared with lansoprazole 30 mg, using the crude rate analysis, were 6.3% and 2.3% in studies 1 and 2, respectively. The absolute difference in EE healing for dexlansoprazole 60 mg compared with lansoprazole 30 mg reached significance only in study 1 ($P < 0.05$). Again, the clinical relevance of the small absolute difference requires further investigation. Using the life-table analysis, there were no significant differences for either dose of dexlansoprazole compared with lansoprazole. In study 1, no dose-response relationship was observed in overall EE healing at week 8 using either the life-table or crude rate analysis. However, rates of EE healing in study 2 using both analyses were numerically higher in the dexlansoprazole 90-mg group

than in the 60-mg group. Thus, the evidence for a dose response is unclear.

In study 1, the rate of healing at week 8 using the life-table and crude rate analyses for patients with EE of LA grade C or D at baseline was significantly higher in the dexlansoprazole 60-mg group compared with the lansoprazole 30-mg group ($P < 0.05$).⁴¹ Using the life-table analysis, the healing rate in the dexlansoprazole 30-mg group was 88.9% (95% CI, 83.7%–94.2%), compared with 74.5% in the lansoprazole group (95% CI, 67.3%–81.6%). Using the crude rate analysis, the healing rate for dexlansoprazole 60 mg was 79.7% (95% CI, 73.1%–85.3%), compared with 65.0% in the lansoprazole group (95% CI, 58.0%–71.6%). Healing rates using the life-table analysis were also significantly higher with dexlansoprazole 90 mg compared with lansoprazole 30 mg in study 1 (83.8% [95% CI, 77.4%–90.1%] vs 74.5% [95% CI, 67.3%–81.6%], respectively; $P < 0.05$). No significant differences were observed in study 2. In a post hoc analysis in which the 2 studies were combined, healing rates in patients with LA grade C or D disease at baseline were significantly higher with dexlansoprazole 90 mg, but not dexlansoprazole 60 mg, compared with lansoprazole 30 mg using both the life-table analysis (88.9% vs 81.5%, respectively; $P < 0.05$) and the crude rate analysis (80.1% vs 71.8%; $P < 0.05$).

The combined safety analysis included all randomized patients who received at least one dose of study medication in the 2 studies ($n = 4092$).⁴¹ One or more treatment-emergent adverse events occurred in 30.4%, 28.1%, and 27.8% of the dexlansoprazole 60-mg, dexlansoprazole 90-mg, and lansoprazole 30-mg groups, respectively. Serious nonfatal adverse events were reported in 22 patients. Four of these were attributed to the study medications: noncardiac chest pain (dexlansoprazole

Table IV. Baseline Los Angeles (LA) classification* of patients with erosive esophagitis in the 2 studies by Sharma et al.⁴¹ Values are number (%) of patients.

Study/Drug	LA Grade				
	A	B	C	D	NA
Study 1					
Lansoprazole 30 mg (n = 690)	231 (33.5)	248 (35.9)	170 (24.6)	40 (5.8)	1 (0.1)
Dexlansoprazole 60 mg (n = 680)	236 (34.7)	247 (36.3)	163 (24.0)	33 (4.9)	1 (0.1)
Dexlansoprazole 90 mg (n = 668)	242 (36.2)	233 (34.9)	148 (22.2)	45 (6.7)	0
Study 2					
Lansoprazole 30 mg (n = 673)	222 (33.0)	257 (38.2)	150 (22.3)	44 (6.5)	0
Dexlansoprazole 60 mg (n = 694)	234 (33.7)	257 (37.0)	156 (22.5)	46 (6.6)	1 (0.1)
Dexlansoprazole 90 mg (n = 687)	271 (39.4)	221 (32.2)	152 (22.1)	42 (6.1)	1 (0.1)

NA = not available.

*The LA classification is used to grade the severity of mucosal damage, with grade A indicating the least severity and grade D indicating the greatest severity.

Table V. Rates of healing of erosive esophagitis at 8 weeks in the 2 studies by Sharma et al.⁴¹

Study/Drug	Healing Rate			
	Life-Table Analysis, % (95% CI)	Absolute Difference Versus Lansoprazole, %	Crude Rate Analysis, % (95% CI)	Absolute Difference Versus Lansoprazole, %
Study 1 (N = 2038)				
Lansoprazole 30 mg	86.1 (83.3–89.2)	–	79.0 (75.6–82.0)	–
Dexlansoprazole 60 mg	92.3 (90.0–94.7)	6.2	85.3 (82.3–87.9)*	6.3
Dexlansoprazole 90 mg	92.2 (89.8–94.6)	6.1	85.8 (82.8–88.4)*	6.8
Study 2 (N = 2054)				
Lansoprazole 30 mg	91.5 (89.0–93.9)	–	84.6 (81.6–87.3)	–
Dexlansoprazole 60 mg	93.1 (90.9–95.3)	1.6	86.9 (84.1–89.4)	2.3
Dexlansoprazole 90 mg	94.9 (92.9–96.8)	3.4	89.4 (86.8–91.7)*	4.8

* $P < 0.05$ versus lansoprazole 30 mg.

60 mg), coronary arteriospasm (dexlansoprazole 90 mg), paralysis (lansoprazole 30 mg), and facial palsy (lansoprazole 30 mg). The pooled incidence of specific adverse events in the dexlansoprazole groups and the lansoprazole group was as follows: diarrhea, excluding infective causes (4.1% and 3.2%, respectively); nausea and vomiting symptoms (2.9% and 2.6%); gastrointestinal and abdominal pain (2.9% and 2.6%); headache (2.9% and 2.3%); upper respiratory tract infection (2.3% and 2.6%); diaphragmatic hernia (1.8% and 1.6%); flatulence, boating, and distention (1.6% and 2.3%); gastritis, excluding infective causes (1.4% and 1.2%); viral infections not otherwise classified (1.2% and 1.0%); and gastrointestinal atonic and hypermotility disorders (1.1% and 1.5%). No statistical comparison was provided. The incidence of premature study discontinuation due to adverse events was 2.3%, 1.3%, and 1.2% in the dexlansoprazole 60-mg, dexlansoprazole 90-mg, and lansoprazole 30-mg groups, respectively. Three patients died in the course of the 2 studies; the cause of death was not reported, but all were considered unrelated to the study medications. Comparable increases in serum gastrin concentrations were reported in patients receiving dexlansoprazole and lansoprazole.

Maintenance of Healed Erosive Esophagitis

Metz et al⁴² conducted a multinational, Phase III, randomized, double-blind study comparing 2 doses of dexlansoprazole with placebo in the maintenance of healed EE. Patients who completed one of the studies by Sharma et al⁴¹ (regardless of their treatment assignment in that study) and had healed EE on endoscopy were randomized to receive dexlansoprazole 30 mg once daily ($n = 140$), dexlansoprazole 60 mg once daily ($n = 158$), or placebo ($n = 147$) for 6 months. There were no significant differences in patients' demographic characteristics at baseline. The incidence of maintained healing of EE at 6 months using the life-table analysis was 74.9%, 82.5%, and 27.2% in the dexlansoprazole 30-mg, dexlansoprazole 60-mg, and placebo groups, respectively. Using the crude rate analysis, the incidence of maintenance of healing at 6 months was a respective 66.4%, 66.4%, and 14.3%. The differences were statistically significant compared with placebo for both the life-table and crude rate analyses and both dexlansoprazole dose groups ($P < 0.001$). The authors reported that there were no significant differences between dexlansoprazole groups on either analysis, but no supporting data were provided.

In a subgroup of patients with LA grades C and D disease at baseline, rates of maintained healing of EE were 63% and 85% for dexlansoprazole 30 mg and dexlansoprazole 60 mg, respectively, using the life-table method ($P = 0.039$).⁴² In patients with LA grade A and B disease at baseline, the corresponding rates of maintained healing were 80% and 82%. Based on patients' daily diaries, the median percentage of 24-hour heartburn-free days was 96%, 91%, and 29% in those receiving dexlansoprazole 30 mg, dexlansoprazole 60 mg, and placebo, respectively ($P < 0.003$, both active treatments vs placebo). The median percentage of nights without heartburn was 99%, 96%, and 72% ($P < 0.003$, both active treatments vs placebo). The median time to recurrence of EE was significantly longer in patients receiving dexlansoprazole 30 or 60 mg compared with those receiving placebo (42, 61, and 30 days; $P = 0.001$ and $P = 0.002$, respectively).

The total score and subscale scores on the diet/food habits, and psychological well-being and distress items of the Patient Assessment of Upper Gastrointestinal Disorders–Quality of Life (PAGI-QOL) questionnaire were reported to be significantly better in the dexlansoprazole 30-mg group compared with the placebo group, although the P value was not reported.⁴³ Only the PAGI-QOL subscale score for diet/food habits was reported to be significantly better in the dexlansoprazole 60-mg group compared with the placebo group. Only the subscale score for heartburn/regurgitation on the Patient Assessment of Upper Gastrointestinal Disorders–Symptom Severity (PAGI-SYM) questionnaire was reported to be significantly better in both dexlansoprazole groups compared with the placebo group.

Forty-eight of the 140 patients in the dexlansoprazole 30-mg group discontinued the study due to relapse ($n = 26$), adverse events ($n = 2$), loss to follow-up ($n = 5$), withdrawal of consent ($n = 11$), and other reasons ($n = 4$).⁴² Fifty-three of the 140 patients in the dexlansoprazole 60-mg group discontinued the study due to relapse ($n = 20$), adverse events ($n = 6$), loss to follow-up ($n = 6$), withdrawal of consent ($n = 17$), and other reasons ($n = 4$). One hundred twenty-two of the 147 patients in the placebo group discontinued the study due to relapse ($n = 81$), adverse events ($n = 8$), loss to follow-up ($n = 5$), withdrawal of consent ($n = 17$), and other reasons ($n = 11$).

The final safety analysis included all randomized patients who received at least one dose of study medication ($n = 445$).⁴² At least one treatment-emergent ad-

verse event occurred in 47%, 53%, and 29% of the dexlansoprazole 30-mg, dexlansoprazole 60-mg, and placebo groups, respectively. The only treatment-emergent adverse event that occurred significantly more frequently in both dexlansoprazole groups compared with the placebo group was upper respiratory tract infection ($P < 0.05$). Because of the large number of relapses and subsequent discontinuations in the placebo group, adverse events were also expressed as the number of patients experiencing the event per 100 patient-months (PM) of exposure. The number of upper respiratory tract infections per 100 PM was 2.2 for dexlansoprazole 30 mg ($n = 14$), 2.4 for dexlansoprazole 60 mg ($n = 17$), and 0.4 for placebo ($n = 1$). There were 1.1 joint-related signs and symptoms per 100 PM in the dexlansoprazole 30-mg group ($n = 7$), significantly more than in the dexlansoprazole 60-mg group, which had no joint-related signs and symptoms ($P < 0.01$). Increases from baseline in median gastrin concentrations at 6 months were 63 pg/mL in the dexlansoprazole 30-mg group and 88 pg/mL in the dexlansoprazole 60-mg group. Biopsy findings at the final visit revealed no signs of intestinal metaplasia with dysplasia, neuroendocrine cell proliferation, or adenocarcinoma.

Howden et al⁴⁴ conducted a multinational, Phase III, randomized, double-blind trial comparing 2 doses of dexlansoprazole with placebo in the maintenance of healed EE. Patients who had completed one of the EE healing studies by Sharma et al⁴¹ and had healed EE on endoscopy were randomized in a 1:1:1 ratio to receive dexlansoprazole 60 mg once daily ($n = 159$), dexlansoprazole 90 mg once daily ($n = 152$), or placebo ($n = 140$) for 6 months. There were no significant differences in demographic characteristics between groups at baseline. Using the life-table analysis, the incidence of maintained healing of EE at 6 months in the dexlansoprazole 60-mg, dexlansoprazole 90-mg, and placebo groups was 86.6%, 82.1%, and 25.7%, respectively. Using the crude rate analysis, the corresponding rates of maintained healing at 6 months were 66.4%, 64.5%, and 14.3%. For both analyses and both treatment groups, the differences were statistically significant compared with placebo ($P < 0.001$). The authors reported that there were no significant differences between the dexlansoprazole groups, although no data were provided.

Based on patients' daily diaries, the median percentage of 24-hour heartburn-free days was 95.8%, 94.4%, and 19.2% in the dexlansoprazole 60-mg, dexlansoprazole 90-mg, and placebo groups, respectively ($P < 0.001$, both

active treatments vs placebo).⁴⁴ The median percentage of nights without heartburn was 98.3%, 97.1%, and 50.0% ($P < 0.001$, both active treatments vs placebo). The mean changes in PGI-QOL and PGI-SYM total scores from day -1 to the final visit were significantly better in both dexlansoprazole groups compared with placebo ($P \leq 0.003$). The mean changes in all PGI-SYM subscale scores (nausea/vomiting, fullness/early satiety, bloating, upper abdominal pain, lower abdominal pain, and heartburn/regurgitation) from day -1 to the final visit were also significantly better in both dexlansoprazole groups compared with placebo ($P \leq 0.003$). Scores on the PGI-QOL daily activities, clothing, diet/food habits, and psychological well-being and distress subscales were significantly better in both dexlansoprazole groups compared with placebo ($P \leq 0.003$). There was no significant difference in the PGI-QOL relationship subscale score between dexlansoprazole 90 mg and placebo; however the difference was significant between dexlansoprazole 60 mg and placebo ($P \leq 0.003$).

Thirty-three patients in the dexlansoprazole 60-mg group discontinued the study.⁴⁴ The reasons for discontinuation were recurrence ($n = 16$), adverse events ($n = 6$), loss to follow-up ($n = 3$), withdrawal of consent ($n = 1$), and other reasons ($n = 7$). Forty-nine patients in the dexlansoprazole 90-mg group discontinued the study. The reasons were recurrence ($n = 13$), adverse events ($n = 9$), loss to follow-up ($n = 4$), withdrawal of consent ($n = 8$), and other reasons ($n = 15$). One hundred twenty-three patients in the placebo group discontinued the study. The reasons were recurrence ($n = 86$), adverse events ($n = 7$), loss to follow-up ($n = 4$), withdrawal of consent ($n = 15$), and other reasons ($n = 11$).

The final safety analysis included all randomized patients who received at least one dose of study medication ($n = 451$).⁴⁴ The incidence of patients prematurely discontinuing study medication due to adverse events was 4%, 6%, and 8% in the dexlansoprazole 60-mg, dexlansoprazole 90-mg, and placebo groups, respectively. The likelihood of patients having at least one treatment-emergent adverse event was significantly higher in the dexlansoprazole 60- and 90-mg groups compared with the placebo group ($P < 0.001$ and $P = 0.003$, respectively). Treatment-emergent adverse events were reported in 79 of 159 patients (50%) receiving dexlansoprazole 60 mg, 66 of 152 (43%) receiving dexlansoprazole 90 mg, and 37 of 140 (26%) receiving placebo. Seven serious nonfatal adverse events were reported, none of them considered related to study medications. Adverse

events occurring at a frequency of $\geq 5\%$ with a higher incidence in either dexlansoprazole group compared with the placebo group were diarrhea (6%, 7%, and $<1\%$, respectively); gastritis (6%, 4%, and $<1\%$); gastrointestinal or abdominal pain (6%, 4%, and 1%); flatulence, bloating, and distention (5%, 2%, and 0%); and upper respiratory tract infection (3%, 7%, and 4%). Again, due to the large number of relapses and subsequent discontinuations in the placebo group, adverse events were expressed as the number of patients experiencing the event per 100 PM of exposure. Using this method of expressing adverse events, diarrhea, gastritis, gastrointestinal or abdominal pain, and flatulence, bloating, and distention occurred more frequently in one or both dexlansoprazole groups compared with the placebo group. However, no statistical analysis was provided.

At 6 months, increases from baseline in median gastrin concentrations were 68 pg/mL in the dexlansoprazole 60-mg group and 77 pg/mL in the dexlansoprazole 90-mg group.⁴⁴ Biopsy findings at the final visit revealed no signs of neuroendocrine cell proliferation, adenocarcinoma, or enterochromaffin-like cell hyperplasia. Intestinal metaplasia was observed in 2.7%, 3.8%, and 3.3% of patients in the dexlansoprazole 60-mg, dexlansoprazole 90-mg, and placebo groups, respectively. Tissue biopsies revealed chronic gastritis in 36.3%, 34.3%, and 29.5% of the respective groups. According to the study protocol, patients with evidence of gastritis were subsequently evaluated for *H pylori*; however, no details of this analysis were provided.

Treatment of Symptomatic Nonerosive Reflux Disease

Fass et al⁴⁵ conducted a multicenter, Phase III, randomized, double-blind study comparing 2 doses of dexlansoprazole with placebo in the treatment of NERD. Eligible patients were aged ≥ 18 years and had heartburn as their primary symptom, heartburn for ≥ 6 months, heartburn on at least 4 of the 7 days before randomization, and no endoscopic evidence of EE. Patients who tested positive for *H pylori* were eligible for enrollment (treatment status was not reported). Eligible patients were randomized in a 1:1:1 ratio to receive dexlansoprazole 30 mg once daily ($n = 315$), dexlansoprazole 60 mg once daily ($n = 315$), or placebo ($n = 317$) for 4 weeks. The primary efficacy end point was the percentage of 24-hour heartburn-free days, as recorded in patients' daily diaries. There were no significant differences in demographic characteristics between groups at baseline. The median percentage of 24-hour heartburn-free days in the dexlansoprazole 30-mg, dexlansoprazole 60-mg, and placebo groups was 54.9%, 50.0%, and 18.5%, respectively ($P < 0.001$, both active treatments vs placebo). There was no significant difference in the median percentage of 24-hour heartburn-free days between the 2 dexlansoprazole doses. Results for the secondary end points are summarized in Table VI.

PAGI-SYM and PAGI-QOL total scores were significantly better in both dexlansoprazole groups compared with the placebo group ($P < 0.005$ and $P < 0.001$, respectively).⁴⁵ Both dexlansoprazole groups also had

Table VI. Results for secondary efficacy end points in patients with symptomatic nonerosive reflux disease in the 4-week study by Fass et al.⁴⁵

End Point	Dexlansoprazole 30 mg	Dexlansoprazole 60 mg	Placebo	<i>P</i> , Both Doses Versus Placebo
Patient-reported days without heartburn, median %	63.0	63.0	26.9	<0.001
24-Hour heartburn-free days in first 3 days of treatment, % of patients	13.9	16.2	2.2	<0.001
Nights without heartburn in first 3 days of treatment, % of patients	38.0	39.8	17.3	<0.001
Days without heartburn in first 3 days of treatment, % of patients	18.5	19.8	8.7	<0.01
Sustained resolution of heartburn at end of treatment, % of patients	59.0	42.0	14.0	<0.001
Days without rescue medication, median %	63.0	63.0	37.3	<0.001

significantly better PGI-SYM subscale scores for heartburn/regurgitation and fullness/early satiety compared with placebo ($P < 0.005$). The PGI-QOL diet/food habits subscale score was significantly better for both dexlansoprazole groups compared with placebo ($P < 0.001$). Data on the other PGI-SYM and PGI-QOL subscale scores were not provided.

The final safety analysis included all randomized patients who received at least one dose of study medication ($n = 947$).⁴⁵ The incidence of patients in the dexlansoprazole 30-mg, dexlansoprazole 60-mg, and placebo groups with at least one treatment-emergent adverse event was 35%, 32%, and 32%, respectively (statistical analysis not provided). Eight serious adverse events were reported (coronary artery occlusion secondary to diabetes, hypertension and hypercholesterolemia, lower abdominal pain and hematochezia, postsurgical cerebrovascular accident, post-myocardial infarction cardiogenic shock, sepsis, and myocardial infarction [2 patients]), none of them considered related to the study medications. Adverse events occurring in $\geq 5\%$ of patients in any treatment group included nausea, diarrhea, and headache (incidence by study group not provided). Discontinuation of study medication and withdrawal due to treatment-emergent adverse events occurred in 1.9%, 2.5%, and 3.5% of patients in the respective groups. Increases from baseline in serum gastrin concentrations at week 4 were 103.6 pg/mL in the dexlansoprazole 30-mg group and 97.0 pg/mL in the dexlansoprazole 60-mg group, significantly greater relative to the 0.9-pg/mL increase in the placebo group ($P < 0.001$). Biopsy findings were not reported.

Treatment of Nocturnal Heartburn in Patients With Symptomatic Nonerosive Reflux Disease

Fass et al⁴⁶ performed a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial of dexlansoprazole 30 mg once daily in 305 patients with nocturnal heartburn. Patients aged 18 to 66 years with moderate to very severe nocturnal heartburn and related sleep disturbances at least 3 days per week were eligible for the study; those with endoscopic evidence of esophageal erosions were excluded. Patients were randomized to receive dexlansoprazole 30 mg once daily in the morning or placebo for 4 weeks. The dexlansoprazole group had a significantly higher percentage of nights without heartburn (the primary outcome) compared with the placebo group (73% vs 36%, respectively; $P < 0.001$). Adverse events were not reported.

Because these data were presented in abstract format, no meaningful conclusions can be drawn.

Concurrently with the previous study,⁴⁶ Orr et al⁴⁷ examined the effects of dexlansoprazole on sleep quality and health-related quality of life (HRQoL) in the same group of patients. At baseline and week 4, patients completed the Pittsburgh Sleep Quality Index (PSQI) and the Nocturnal Gastroesophageal Reflux Disease Symptom Severity and Impact (NGERD) questionnaire, both validated instruments. Lower scores on these instruments indicate better sleep quality and better control of GERD symptoms, respectively. At week 4, patients receiving dexlansoprazole 30 mg once daily had significant improvements in mean (SD) PSQI scores compared with those receiving placebo (6.60 [3.71] vs 7.52 [3.70], respectively; $P < 0.001$). NGERD total HRQoL scores were also significantly improved in the dexlansoprazole 30-mg group compared with the placebo group at week 4 (18.17 [19.34] vs 30.23 [22.11]; $P < 0.001$).

Johnson et al⁴⁸ conducted a concurrent analysis of the effect of dexlansoprazole on work productivity and daily activities in the 305 patients in the study by Fass et al.⁴⁶ The validated Work Productivity and Activity Impairment-Specific Health Problem questionnaire, on which higher scores indicate greater impairment and less productivity, was completed at baseline and week 4. At baseline, overall mean (SD) work productivity scores in the dexlansoprazole 30-mg and placebo groups were 38.08 (29.03) and 40.99 (27.77), respectively. At week 4, mean scores were a respective 13.04 (19.94) and 23.93 (26.47). The difference between dexlansoprazole and placebo was significant at week 4 ($P = 0.003$).

Pooled Gastric Biopsy Results

Bronner et al⁴⁹ performed a pooled analysis of all available gastric biopsy results from the clinical and safety studies of dexlansoprazole. Biopsy results from baseline and the final visit were available for 446 patients assigned to dexlansoprazole and only 140 patients assigned to placebo; the small number of placebo recipients with complete biopsy data was a result of the large number of withdrawals from the placebo group in the studies of maintenance of EE healing. Antral reactive gastropathy was observed in 9.2% of patients who received dexlansoprazole 90 mg and 2.3% of patients who received placebo ($P \leq 0.05$). Fundic chronic gastritis with *H pylori* was observed in significantly more patients in the placebo group compared with the dexlansoprazole 90-mg group (6.5% vs 1.0%, respectively; $P \leq 0.05$).

The most commonly reported abnormality in both groups was chronic gastritis (antral or fundic), which occurred in 30% to 34% of those who received dexlansoprazole and 33% of those who received placebo. Endocrine-cell hyperplasia, adenocarcinoma, and lymphoma were not reported in any patients.

DOSING AND ADMINISTRATION

Dexlansoprazole is available as 30- and 60-mg capsules. The recommended dose for the healing of EE is 60 mg once daily for up to 8 weeks.²² The recommended dose for the maintenance of healed EE is 30 mg once daily, with the duration of therapy not to exceed 6 months. The dose for symptomatic NERD is 30 mg once daily for 4 weeks.

In patients with moderate hepatic impairment (Child-Pugh Class B), the maximum recommended dose is 30 mg once daily²²; there are currently no dosing recommendations for patients with severe hepatic impairment. Dexlansoprazole may be taken without regard to food. In patients who are unable to swallow whole capsules, dexlansoprazole may be administered by opening the capsule and sprinkling the intact granules over one tablespoon of applesauce, which should be ingested immediately.

PHARMACOECONOMIC CONSIDERATIONS

No cost-effectiveness analyses or other pharmacoeconomic assessments of dexlansoprazole were identified by the literature search. In the United States, the average cost to patients for a 30-day supply of dexlansoprazole 30- and 60-mg capsules is \$127.98.⁵⁰ Although the therapeutic effects of PPIs may be comparable, their cost can be extremely variable. The differences in cost are influenced by the availability of generic and/or over-the-counter (OTC) formulations and the desired dosage form. The cost of dexlansoprazole is higher than that of generic and/or OTC preparations of omeprazole, pantoprazole, and lansoprazole. Nevertheless, the overall monthly cost of dexlansoprazole is less than that of branded esomeprazole or rabeprazole. Table VII provides a cost comparison of PPIs currently available in the United States.

DISCUSSION

One of the greatest challenges with the currently available therapies for EE is the maintenance of gastric acid suppression. Failure to maintain suppression of gastric acid is among the reasons why 10% of patients with

EE do not respond after 8 weeks of PPI therapy, and lack of sustained gastric acid suppression may also contribute to the 40% failure rate in patients with NERD after 4 weeks of PPI therapy.^{4,11,12} The dual delayed-release formulation of dexlansoprazole provides 2 distinct peaks, leading to more prolonged acid suppression compared with lansoprazole, which has only a single peak.^{25,26}

While the dual delayed-release formulation prolongs concentrations of active drug, it is not without limitations. In pharmacokinetic studies, the first peak was found to occur 1 to 2 hours after administration and the second peak 4 to 5 hours after administration.²⁵ Therefore, the second peak comes ~2 to 4 hours after the first peak, whereas it would be ideal for the 2 peaks to be more evenly distributed, mimicking twice-daily dosing. However, delaying the second release would likely result in drug release beyond the ileocecal junction in the colon, which would affect the absorption of dexlansoprazole.⁵¹

An important surrogate marker of mucosal healing in patients with EE is the percent of time that the pH is >4. In the combined analysis by Vakily et al,²⁵ patients receiving dexlansoprazole 30 and 90 mg once daily for 5 days had a mean intragastric pH >4 for 59.2% and 66.7% of a 24-hour period, respectively. In a 5-way crossover study of esomeprazole 40 mg, rabeprazole 20 mg, omeprazole 20 mg, lansoprazole 30 mg, and pantoprazole 40 mg, each given for 5 days, in 34 patients with symptoms of GERD,⁵² the mean intragastric pH (measured over 24 hours) was >4 for 58.43%, 50.53%, 49.16%, 47.98%, and 41.94% of the time in the respective groups on day 5. Thus, the percent of time the pH was >4 with dexlansoprazole 30 and 90 mg was comparable to that reported for the other PPIs currently available in the United States.

The current lack of head-to-head comparative clinical trials makes it difficult to determine dexlansoprazole's relative place among PPIs. One of the randomized, double-blind studies by Sharma et al⁴¹ found that dexlansoprazole was better than lansoprazole in healing more severe EE (LA grades C and D), although the other study did not confirm this finding. A combined post hoc analysis of these 2 studies, conducted to increase statistical power, found that dexlansoprazole 90 mg, but not 60 mg, significantly improved rates of EE healing in patients with LA grades C and D disease at baseline compared with lansoprazole 30 mg once daily ($P < 0.05$).⁴¹ An adequately powered study conducted exclu-

Table VII. Cost comparison of currently available proton pump inhibitors.⁵⁰

Drug	Availability	Cost per Month*
Dexlansoprazole	30- and 60-mg capsules No generic or OTC formulation available	\$127.98
Esomeprazole	20- and 40-mg capsules 10-, 20-, and 40-mg suspension 20- and 40-mg injection No generic or OTC formulation available	20-mg capsules: \$181.29; 40-mg capsules: \$162.99
Lansoprazole	15- and 30-mg capsules, suspension, and orally disintegrating tablets 30-mg injection Generic and OTC (15 mg) formulations available	Brand: 15-mg capsules, \$169.99; 30-mg capsules, \$176.38 Generic: 15- and 30-mg capsules, \$99.99
Omeprazole	10-, 20-, and 40-mg capsules Generic and OTC (20-mg tablets) formulations available Available in combination with sodium bicarbonate	Brand: 20-mg capsules, \$459.99; 40-mg capsules, \$250.37 Generic: 20-mg capsules, \$32.99; OTC 20-mg tablets, \$27.85; 40-mg capsules, \$170.01
Pantoprazole	20- and 40-mg tablets 40-mg suspension 40-mg injection Generic formulation available; no OTC formulation available	Brand: 20-mg tablets, \$140.47; 40-mg tablets, \$138.37 Generic: 20- and 40-mg tablets, \$109.99
Rabeprazole	20-mg tablets No generic or OTC formulation available	\$194.56

OTC = over-the-counter.

*Costs may vary based on the formulation. Prices were identified for oral formulations (tablets and/or capsules) only.

sively in patients with LA grades C and D disease is needed to confirm any potential advantage in this subset of patients. Esomeprazole would be the active comparator of choice, as there are data suggesting that this agent is more effective for EE healing than other PPIs.¹³

The long-term safety of newly approved medications is always a concern. Given the available data from clinical studies, dexlansoprazole appears to be well tolerated, with an acceptable safety profile. Gastric biopsy results were provided in some of the healing, maintenance, and safety studies; because of the small number of abnormalities, it is difficult to determine their impact on a study-by-study basis. A pooled analysis found no clinically significant pathologic findings in evaluable dexlansoprazole recipients (n = 446).⁴⁹ For a pooled analysis, the sample of evaluable patients was small, and postmarketing surveillance will be crucial to detecting any long-term safety concerns with dexlanso-

prazole. However, the clinical experience with PPIs in the United States spans more than a decade and supports their safety as a class.

CONCLUSIONS

In Phase III clinical trials, dexlansoprazole was associated with significantly better maintenance of EE healing, as well as improved outcomes in patients with NERD, compared with placebo. Dexlansoprazole was statistically noninferior to lansoprazole in terms of rates of EE healing. Dexlansoprazole appeared to be well tolerated; however, the longest clinical trial was only 6 months in duration, and postmarketing surveillance is needed to elucidate any long-term concerns. With its unique dual delayed-release formulation, dexlansoprazole has a modest theoretical advantage over currently available PPIs. However, more head-to-head comparative trials with other PPIs are needed to determine

whether this theoretical advantage translates into a clinically significant improvement compared with the current standard of care.

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