

REVIEW

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Dexlansoprazole MR in the Management of Gastroesophageal Reflux Disease

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Abstract: Dexlansoprazole MR, an enantiomer of lansoprazole, is a unique proton pump inhibitor with a dual release mechanism. This release mechanism produces two distinct peak concentrations that result in a prolonged mean residence time with increased duration of plasma concentrations and a greater percent time the pH is maintained above 4. The prolonged residence time allows dexlansoprazole MR to be administered throughout the day without regards to meals or the timing before a meal. In two trials of patients with erosive esophagitis, dexlansoprazole MR 60 mg and 90 mg demonstrated comparable healing rates to lansoprazole 30 mg. In patients with healed EE, dexlansoprazole MR 30 mg (75%) and 60 mg (83%) were superior to placebo (27%; $p < 0.0025$) in maintenance of healing. Dexlansoprazole MR 30 mg and 60 mg had a greater percentage of heartburn-free days (91%–96%) and heartburn-free nights (96%–99%) than placebo (29%–72%) over the 6-month maintenance trial. Dexlansoprazole MR appears to be well tolerated with the safety profile being similar to lansoprazole with gastrointestinal adverse events being the most common. Dexlansoprazole MR provides a new treatment option for gastroesophageal reflux disease due to the flexible dosing, the unique release mechanisms and prolonged pharmacodynamic effect.

Keywords: dexlansoprazole MR, GERD, proton pump inhibitors, lansoprazole, esomeprazole, omeprazole, pantoprazole, rabeprazole

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Introduction

Pharmacotherapy with proton pump inhibitors (PPIs) as opposed to other acid suppressive agents has radically improved the treatment efficacy over histamine receptor antagonists in acid related disorders, such as gastroesophageal reflux disease (GERD).^{1,2} The PPIs are potent blockers of acid secretion from parietal cells and significantly raise gastric pH compared to histamine receptor antagonists or antacids.³ Unlike other agents, tolerance does not develop to the acid blocking ability of the PPIs as they are able to consistently provide acid suppression over prolonged (months to years) periods of time. Thus, the PPIs have become the gold standard for treatment of reflux related diseases and not only do they improve efficacy, but they are generally safe, well tolerated pharmacologic agents.⁴

Proton pump inhibitors are not without limitations. Both delayed release (DR) and immediate release (IR) technology PPIs have relatively rapid delivery of drug in the small intestine for absorption into the systemic circulation and an equally rapid elimination process through a combination of renal excretion and hepatic metabolism.⁵ The results are short half-lives of approximately 2-hours and mean-residence-time (time drug remains in the serum or plasma) of 5 to 6 hours that results in limited exposure of the proton pump to inhibition by the various PPIs. Because of this short exposure and despite the irreversible binding of PPIs to the proton pump, PPIs are unable to achieve complete acid control over a 24-hour period following single and multiple oral doses. This has resulted in inadequate symptom control and a higher incidence of treatment failures, especially in those patients with more severe gastroesophageal reflux disease (GERD). In several trials, patients with advanced disease experienced less than 70% complete symptom relief and up to a 30% failure in healing of erosive lesions in the lower esophagus.⁴ Multiple factors are likely to explain these treatment failures, but there is evidence that not all proton pump inhibitors have the same intrinsic binding capacity to proton pumps and therefore differ in the ability to raise gastric pH over a 24-hour period.⁶ In an attempt to improve acid suppression of PPIs, clinicians have given larger single doses or administered the drugs multiple times a day. These attempts do increase pH values, but doubling

a dose significantly increases the cost of therapy and twice daily therapy has been shown to result in non-compliance and treatment failures. In addition, doubling a dose significantly increases the peak serum concentration, but overall duration of exposure to the proton pump is approximately the same. Thus, doubling the dose may be less effective than taking a PPI twice daily. Pharmaceutical manufacturers have also made various changes in dosage formulations and use of enantiomer products to increase duration of pH control and ultimately to increase the efficacy of certain PPIs.

Dexlansoprazole modified release (MR) is the newest PPI formulation on the US market that is not only a delayed release (DR) compound, but utilizes dual drug release (DDR) technology that results in a biphasic release and absorption.^{7,8} The result is an increase in the area under serum concentration (AUC) time-curve and more prolonged exposure of the drug to the proton pumps found in the parietal cell. Dexlansoprazole MR was approved in early 2009 by the United States Food and Drug Administration (FDA) for the healing of all grades of erosive esophagitis (EE; 60 mg once daily for up to 8 weeks), for maintaining healing of EE (30 mg once daily for up to 6 months), and for the treatment of heartburn associated with non-erosive gastroesophageal reflux disease (NERD; 30 mg once daily for 4 weeks). This review will discuss differences in PPI pharmacology and dosage forms and compare and evaluate dexlansoprazole MR efficacy and safety in treating EE and NERD.

Dexlansoprazole MR and PPI Formulations and Properties

When given as a racemic mixture of R and L enantiomers (lansoprazole), the R enantiomer is responsible for approximately 80% of the total drug reaching the systemic circulation. Dexlansoprazole MR a new proton pump inhibitor formulation with a dual drug release (DDR) consists only of the R-enantiomer of lansoprazole.⁹ Dexlansoprazole MR is supplied in 30 mg and 60 mg capsules that contain a mixture of two different enteric coated granules that have dissimilar pH dependent dissolution profiles. Like most other PPIs that are classified as delayed release (DR) formulations, dexlansoprazole



MR releases drug from the enteric coated granules. However, dexlansoprazole MR differs in that the release follows a bimodal fashion that is designed to prolong the serum concentration and increase exposure to the proton pumps once it is absorbed. All other PPIs employ a single-release mechanism whether they are a delayed release (DR) or immediate release (IR) formulation. All DR compounds are enteric coated in order to protect the PPI from activation prior to absorption. Only one formulation uses the IR design. This is the combination of omeprazole and sodium bicarbonate where the bicarbonate raises gastric pH and prevents activation of the parent PPI compound prior to absorption. In comparison, the DDR technology produces a dual peak pharmacokinetic profile which results in an extended duration of exposure compared to the single peak associated with IR and DR PPIs.

Pharmacology

Mechanism of action

Gastric acid secretion is a multifaceted process regulated by three receptors (gastric, histamine and acetylcholine) found in the parietal cell. No matter what the triggering receptor, all pathways for gastric acid secretion lead to the proton pump or $H^+K^+ATPase$ found in the canaliculus area of the parietal cell.³ The proton pump represents the final pathway to acid release into the stomach lumen. Therefore inhibition of these pumps results in significant reduction in acid secretion. All proton pump inhibitors (PPIs) work by relatively the same mechanism in that they enter the parietal cell and irreversibly bind to the pumps to collectively shut off acid secretion in to the gastric lumen. However, the mechanism is more complicated than simply binding the pumps. This fact has led to multiple different PPI products and formulations in attempt to maximize the magnitude and duration of proton pump inhibition. The chemical structure of all PPIs consists of pyridine and benzimidazole rings with a sulfenamide (sulfenic acid) moiety in the parent structure. The sulfenic acid moiety is not reactive enough to form the disulfide bonds on cysteine residues of the proton pump and therefore must first be activated through 2 protonations and a subsequent spontaneous rearrangement to form the sulfenamide derivative. Thus, in order for

the PPI to inhibit the pump, it must be converted to the sulfenamide moiety before binding to the cysteine residues. The PPIs are activated at various levels of pH which is illustrated by the pKa value (Table 1).¹⁰ When the environment is less acidic, or has a higher pKa, the PPI chemical structure is more willing to accept a proton and become activated. Rabeprazole has the highest pKa and is therefore the most likely of all the PPIs to be activated if exposed to stomach acid. Once the PPI is swallowed, the enteric coating slowly dissolves and allowing release of the drug in the small intestine for absorption. In order for the PPIs to inhibit the proton pump, they must enter the parietal cell in an inactive form. On exposure to acid in the canaliculus area, the PPIs are converted to their active moiety. Therefore, the PPI in the parietal cell, now in the active sulphenamide form, is able to bind onto the proton pump irreversibly, regardless of how stable the parent compound is. To achieve the maximum acid suppression, a PPI must concentrate in a parietal cell when the maximum numbers of pumps are actively secreting acid.¹¹

Most proton pump inhibitors formulations exist as delay release (DR) enteric coated granules (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole) and immediate release (IR) (omeprazole in sodium bicarbonate) products. A common misconception is the concept of PPI destruction by gastric acid. If PPIs are exposed to gastric acid prior to their delivery to the parietal cell, or more specifically in the stomach, protonation occurs and the active moiety is formed. The PPI compounds that are activated in the stomach would non-selectively bind to cysteine residues found on the proteins of stomach epithelium cells which would in turn reduce absorption and ultimately bioavailability. The sodium bicarbonate found in the only IR PPI protects the chemical structure from acid activation and like the DR products are delivered past the pylorus into the higher pH (near pH 7) of small intestine in the inactive form.^{5,12} For maximal acid suppression DR PPI compounds are recommended to be administered approximately 15 to 60 minutes before the morning meal to assure the maximum numbers of pumps are activated at the time the drug reaches the parietal cell. Unfortunately, the PPIs have short half-lives (approximately 2-hours) and short mean-residence



Table 1. Comparative pharmacokinetic data of proton pump inhibitors.^{13–16,19,36–51}

Pharmacokinetic parameter	Dexlansoprazole MR 60 mg	Esomeprazole 40 mg	Lansoprazole 30 mg	Omeprazole 20 mg	Omeprazole/Sodium Bicarbonate 40 mg	Pantoprazole 40 mg	Rabeprazole 20 mg
T_{max} (h)	5.03	1.6	1.3–2.2	1–3	0.5	2–4	3.1
C_{max} ($\mu\text{g/mL}$)	1.29	4.7	0.6–1.2	0.08–8	1.53–1.95	1.1–3.3	0.41
AUC ($\mu\text{g}\cdot\text{h/mL}$)	6.533	3.314	1.7–5	0.2–1.2	1.665–3.356*	2–5	0.8
$t_{1/2}$ (h)	1.49	1.5	0.9–1.6	0.6–1	1.0	0.9–1.9	1
pKa	NA	4.13	4.01	4.13	4.13	3.96	5.0
Oral Bioavailability (%)	NA	64	80–91	35–40	30–40	77	NA

Abbreviations: *1st and 2nd dose AUCs; T_{max} , time to maximum serum concentration; h, hours; C_{max} , maximum serum concentration; AUC, area under the curve; $t_{1/2}$, half-life; NA, not available.

times that only allow inactivation of pumps over a narrow window after drug absorption. The IR formulation allows for more liberal dosing without regards to a meal since the bicarbonate stimulates the proton pumps, but still possess a similar mean-residence time to the DR products and exposes patients to increased loads of sodium which may complicate treatment of some cardiovascular and renal disorders.

Dexlansoprazole MR is a unique DR release product that provides prolonged residence time combined with an increase AUC to allow once daily dosing. Because the drug has prolonged exposure to parietal cells, it can be given without regards to meals, unlike the other DR PPIs and potentially may improve the acid suppression pharmacodynamics which is closely related to healing.

Pharmacokinetics

The PPIs have relatively short half lives at approximately 1–2 hours which suggests that they are unlikely to accumulate in the systemic circulation.¹³ The AUCs are reported to correlate well with acid suppression.¹⁵ The AUC for omeprazole 20 mg (0.2–1.2 $\mu\text{g}\cdot\text{h/mL}$) and rabeprazole 20 mg (0.8 $\mu\text{g}\cdot\text{h/mL}$) are much lower than the AUCs for pantoprazole 40 mg (2–5 $\mu\text{g}\cdot\text{h/mL}$), omeprazole/sodium bicarbonate (1.665 $\mu\text{g}\cdot\text{h/mL}$), lansoprazole (1.7–5 $\mu\text{g}\cdot\text{h/mL}$), and esomeprazole (3.314 $\mu\text{g}\cdot\text{h/mL}$) (Table 1).¹³ The oral bioavailabilities of the proton pump inhibitors are all very different. Omeprazole is 35%–40% bioavailable with the first dose but increases to 65% with repeated doses. Pantoprazole is constant at 77% and lansoprazole is constant at 80%–91% bioavailable, although neither of these is dependent on the dose. The systemic availability for esomeprazole is 64% after a single dose, then increases to 90% after multiple doses over a 5-day regimen.¹⁴ The bioavailability for omeprazole/sodium bicarbonate is approximately 30%–40%.¹⁵

The AUC for dexlansoprazole MR is 2–5 times higher than the AUC for the other PPIs. The mean C_{max} values are higher than most PPIs with the exception of IR omeprazole. The T_{max} is around 1.5–5 times longer than most of the other PPIs and 10 times higher than that of the IR omeprazole. The extended T_{max} and the higher plasma concentrations indicate that the duration of drug exposure is extended with the dexlansoprazole MR.¹⁶ Dexlansoprazole MR has a fairly short half-life of around



1.5 hours which is comparable to lansoprazole and the other PPIs which also suggests little accumulation. The extended release technology makes up for the short half-life by delaying the T_{max} , but results in a significantly larger AUC. The PK profile of dexlansoprazole MR following oral administration shows two peaks, one at around 1–2 hours that is consistent with the peak for lansoprazole and the second at 4–5 hours.^{8,16}

Food has variable effect on the absorption characteristics and bioavailability of PPIs. When given with a meal all PPIs experience a delay in absorption with peak serum concentrations occurring as long as two to four hours post-dose. In addition, some PPIs (esomeprazole, lansoprazole, omeprazole) experience decreases in area under the curve ranging from 33%–50%. The effect of food on dexlansoprazole MR was evaluated in an open-label, single dose, randomized, 4-way cross over study in 48 healthy subjects.¹⁷ Patients received in randomized cross-over fashion, placebo or dexlansoprazole MR 90 mg on either day 1 or day 3 after fasting, at 5 or 30 minutes before a high fat breakfast or 30 minutes after a high fat breakfast. The pharmacodynamic response was determined by intragastric pH measurements on each respective study day and blood samples for pharmacokinetics parameters were obtained on day 3 of dexlansoprazole MR therapy, both over a 24-hour period. Dexlansoprazole MR experienced an increased absorption with the fed regimens with higher maximum plasma concentrations (12%–31%) and area under the plasma concentration-time curve (9%–21%). However, the differences in the gastric pH profiles were considered clinically irrelevant. Therefore, dexlansoprazole MR can be given without regards to food in most patients which may be a clinical advantage over other delayed released PPIs.

Dexlansoprazole MR is extensively metabolized by the liver through oxidation, reduction and conjugation to form various inactive metabolites.⁷ Approximately 50% of drug is excreted unchanged in the urine. In a study conducted in 12 patients with moderate hepatic impairment, the dexlansoprazole MR AUCs were approximately two times greater than patients with normal liver function. In patients with Child-Pugh Class B, a maximum dose of dexlansoprazole MR 30 mg should be considered.⁷ There are no data available in patients with more severe liver impairment.

Pharmacodynamics

The benchmark comparator for PPIs is the percentage of time the intragastric pH remains above 4 during the 24-hour period following an oral dose. This duration has been used to predict clinical efficacy with PPIs in the treatment of EE and GERD.¹⁸ The pharmacodynamics of dexlansoprazole MR compared to lansoprazole have been evaluated in two separate open label, multiple dose, crossover studies in healthy subjects.⁹ The two studies used doses of dexlansoprazole MR ranging from 60 mg to 120 mg and lansoprazole doses of 15 mg and 30 mg orally administered for 5 consecutive days at approximately 9 AM each day following an overnight fast. Patients received standard diets starting one hour post-dose. Intragastric pH was measured continuously on days 1 and 5 with parameters assessed that included mean 24-hour gastric pH and percent time gastric pH remained >4 for the 24-hour post-dose interval. Dexlansoprazole MR at all doses, including the marketed 60 mg capsule, compared to lansoprazole 30 mg, demonstrated significantly higher AUCs (Fig. 1), and superior control of intragastric pH on day 5 of the study. Dexlansoprazole MR 60 mg compared to lansoprazole 30 mg was able to produce a higher intragastric pH (pH 4.55 vs. 4.13), a longer percent (71% vs. 60%) of time intragastric pH was > 4 and a greater mean hours (17 hours vs. 14 hours) the gastric pH remained > 4.

Currently there are no comparative studies that contrast the pharmacodynamics of all DR PPIs (esomeprazole, omeprazole, pantoprazole, rabeprazole, lansoprazole, and dexlansoprazole MR) or IR PPIs (omeprazole and sodium bicarbonate). Using data obtained from product labels, (Table 2) it appears dexlansoprazole MR is comparable to other PPIs in the ability to maintain gastric pH > 4 and the mean 24-hour gastric pH post-dose. The duration of all the PPIs are more reflective of their irreversible binding to proton pump given their short half-lives and residence times.^{7,14,19–22} Since these data are not taken from the same study, they are not completely comparable. For example, in the two different product labels with lansoprazole, significantly different results are reported.^{7,21}

Metabolism and Drug Interactions

All PPIs undergo some degree of hepatic metabolism through cytochrome (CYP) isoenzymes.²³ The enzymes involved in PPI metabolism include CYP3A and

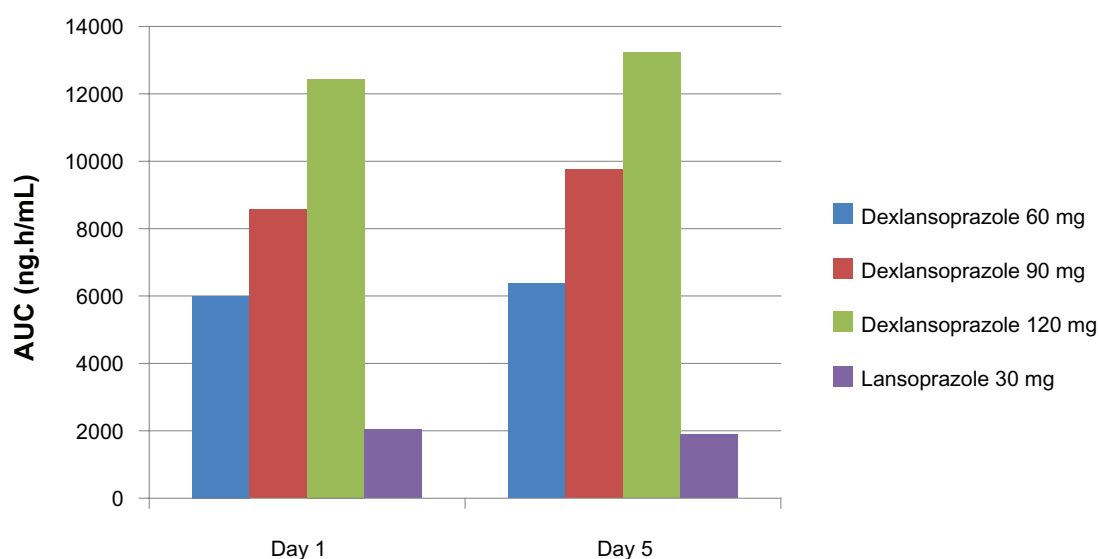


Figure 1. Comparison of days 1 and 5 dexlansoprazole MR and lansoprazole AUCs (n = 40).

polymorphic CYP2C19. All the PPIs have variable affinity for the enzymes, although omeprazole is the most rapidly and extensive metabolized by both aforementioned enzymes. Omeprazole has been associated with drug interactions related to enzyme inhibition with significantly reduced diazepam (25% to >50%) and phenytoin (up to 15%) clearance.²³ Esomeprazole, the S-enantiomer of omeprazole, has a similar effect on diazepam clearance.¹⁴ Other PPIs, such as lansoprazole and pantoprazole have limited drug interactions which are likely related to their low affinity for hepatic CYP isoenzymes.^{20,21,23}

Dexlansoprazole MR, as with lansoprazole, is primarily metabolized through the same enzyme pathways, CYP3A and CYP2C19.³ Since dexlansoprazole MR utilizes higher doses and has prolonged plasma concentration-time profile, the potential for inhibition of CYP isoenzymes may be greater than with lansoprazole. Dexlansoprazole MR was evaluated in

healthy volunteers in four randomized, double blind, two-way cross over drug interactions studies.²⁴ Four test drugs with narrow therapeutic spectrums, diazepam, phenytoin, theophylline and warfarin were assessed with 90 mg dexlansoprazole MR or placebo over 9 to 11 days duration. These studies were designed to evaluate the impact of dexlansoprazole MR on the pharmacokinetics of each agent. The results from these studies indicated similar pharmacokinetics in the control groups and the dexlansoprazole MR groups. Thus, it is unlikely that dexlansoprazole MR will significantly alter the pharmacokinetics of these drugs or others agents metabolized by CYP2C19, CYP2C9 or CYP1A2 isoenzymes.²⁴

Safety

All PPIs are generally well tolerated by most patients. Common adverse effects among all proton pump inhibitors include headache, diarrhea, rash, nausea,

Table 2. Pharmacodynamic parameters for various PPIs obtained from the respective product labels.^{7,14,19–22}

	Dexlansoprazole MR 60 mg	Esomeprazole 40 mg	Lansoprazole 30 mg*	Omeprazole/Sodium Bicarbonate IR 40 mg	Rabeprazole 20 mg
Time in hours gastric pH > 4 over 24-hours	17	16.8	14/15.8	18.6	14.4
Percentage of Time gastric pH > 4	71	70	60/66	77	60
Mean gastric pH	4.55	4.9	4.13/4.9	5.2	3.5

*data taken from Prevacid and Kapidex labels.



and constipation with incidences of 1%–3%. Serious adverse effects are very uncommon with PPIs.¹³ Recent reports have associated proton pump inhibitors with increased community acquired upper respiratory tract infections and pneumonia, hip fracture from reduced calcium absorption, *Clostridium difficile* infection, vitamin B12-deficiency and renal impairment are of concern.^{25–27} The link of PPIs to these adverse events is controversial as others have questioned the relationship. The relationships of dexlansoprazole MR to these AEs is unknown but reasonable caution should be given as with any PPIs. The longer residence time and higher pH associated with dexlansoprazole will warrant follow-up safety studies to assess the risk of serious adverse events that may be associated with PPIs.

A comparison of lansoprazole to dexlansoprazole MR safety data from published clinical trials was compiled and compared (Table 3). The data was obtained from the results of two randomized EE studies and two clinical trials of maintenance of healed EE. The incidence of most adverse events

was indistinguishable from the placebo treatment group. In addition, there were no clinically significant differences observed in the percentage of patients that experienced side effects outside the normal range between lansoprazole and the two doses of dexlansoprazole MR. The dexlansoprazole MR 30 mg dose had slightly lower AEs compared to the 60 mg and 90 mg doses.^{16,28–30}

The elevation of gastrin following prolonged therapy with PPIs is well known. In response to decreased gastric acid secretion by PPIs, increased plasma gastrin levels are observed. Prolonged excess gastrin exposure has led to hyperplasia and tumors of enterochromaffin-like cells (ECL) in rodent models. Despite these observations, there is no evidence of gastric hyperplasia, neoplasia or carcinoid formation in humans following short or long term PPI therapy. Given the interest in gastrin concentrations during PPI therapy, dexlansoprazole MR was evaluated among healthy subjects and within the multicenter clinical trials. Zhang and colleagues evaluated the impact on gastrin levels by dexlansoprazole MR 90 mg and

Table 3. Comparative adverse events between dexlansoprazole MR and lansoprazole obtained from published clinical trials.^{28,29,33}

Adverse event	Placebo (n = 287) n (%)	Dexlansoprazole MR 30 mg q.d.s (n = 140) n (%)	Dexlansoprazole MR 60 mg q.d.s. (n = 1691) n (%)	*Dexlansoprazole MR 90 mg q.d.s. (n = 1507) n (%)	Lansoprazole 30 mg q.d.s. (n = 1363) n (%)
Diarrhea (excluding infective)	2 (0.7)	5 (0.3)	75 (4.4)	65 (4.3)	44 (3.2)
Nausea and vomiting symptoms	NR	NR	40 (2.3)	47 (3.1)	26 (2.6)
Gastrointestinal and abdominal pain	7 (0.2)	3 (0.2)	53 (3.1)	47 (3.1)	35 (2.6)
Headache, Musculoskeletal pain	6 (0.2)	3 (0.2)	51 (3.0)	44 (2.9)	32 (2.3)
Upper respiratory tract infections	6 (0.2)	14 (10)	55 (3.2)	36 (2.4)	36 (2.6)
Flatulence, bloating and distension	7 (0.2)	3 (0.2)	33 (1.9)	23 (1.5)	32 (2.3)
Diaphragmatic hernias	NR	NR	25 (1.5)	25 (1.7)	22 (1.6)
Gastritis (excluding infective)	10 (0.3)	2 (0.1)	41 (2.4)	20 (1.3)	16 (1.2)
Gastrointestinal atonic and hypermotility disorders NEC	NR	NR	24 (1.4)	17 (1.1)	20 (1.5)
Viral infections NEC	NR	NR	17 (1.0)	21 (1.4)	13 (1.0)

*Not available in the U.S.

Abbreviations: q.d.s., once daily; NEC, not elsewhere classified; NR, not reported.



120 mg for 5 days compared to lansoprazole 30 mg in 42 healthy volunteers.³¹ The mean plasma gastrin concentrations were higher after administration of all three medications compared to baseline values. The mean gastrin values were similar between all regimens both on day 1 and day 5. However, post-hoc analysis did not demonstrate a clear dose-dependent relationship on either day.³² In contrast, Sharma et al reported similar increases in gastrin plasma concentrations in the two large trials of EE treatment. In this report, the dexlansoprazole MR groups had higher values than the lansoprazole treatment group.²⁸ All groups were within the range expected with PPI treatment.²⁸ In long term (6 month) maintenance of healing trials, dexlansoprazole MR 60 mg and lansoprazole 30 mg both produced increases in plasma gastrin (88 pg/mL and 63 pg/mL, respectively).³³ As previously outlined, some patients treated in the EE trials were given placebo in the maintenance of healing trials. For patients that received either dexlansoprazole MR or lansoprazole as part of the healing trials and then given placebo for the maintenance of healing trials, all returned to baseline gastrin levels within one month of discontinuation of PPI treatment. Gastrin values reported in the dexlansoprazole MR clinical trials were consistent with previous reports with pantoprazole and omeprazole.¹³

Efficacy

The goals of GERD treatment consist of improving day and night time symptoms, improvement in quality of life, healing and maintenance of erosive esophagitis (EE) and prevention of complications. Previous studies have determined that PPIs are the preferred acid suppressive therapy for initial treatment of EE. Thus, for efficacy studies, another PPI is generally used as the comparative agent.

Erosive Esophagitis (EE)

Dexlansoprazole MR has been evaluated in two randomized control trials that assessed the efficacy and safety in healing erosive esophagitis (Table 4).²⁸ Both studies were designed as non-inferiority and superiority comparing the dexlansoprazole MR groups to lansoprazole. The sample size provide at least 95% power at the 0.025 level of significance to meet non-superiority criteria while the sample size at 80% power at the 0.025 level of significance was able to detect a 6% difference for superiority in healing rates

at 8 weeks. A total of 4092 patients were enrolled in the two double-blind trials that randomized patients to receive either 60 mg or 90 mg dose of dexlansoprazole MR or lansoprazole 30 mg every day for 8-weeks. Patients who tested positive for *Helicobacter pylori* were excluded from the trial. All patients underwent endoscopy prior to randomization to confirm EE with a 30% goal of moderate to severe EE (LA classification grades C and D). The efficacy endpoints were the percent of patients who had complete EE healing at 8 weeks as assessed by endoscopy. Secondary endpoints included percent of patients who had complete healing at 4 weeks as assessed as by endoscopy and the percentage of patients with LA grades C and D EE who demonstrated complete healing at week 8 following endoscope assessments. Other assessment variables included percentage of days free of day-time or night-time heartburn (evaluated by daily diary logs), percentage of patients with sustained (7 consecutive days) heart-burn free days, percentage of days with rescue medication use and severity of symptoms.

Both doses of dexlansoprazole MR achieved non-inferiority to lansoprazole in the two trials. After life-table analysis, dexlansoprazole MR healed 92%–95% of patients while lansoprazole healed 86%–92% in the two respective studies ($p > 0.025$). The groups were also similar in healing at the 4-week analysis suggesting there were no differences in how quickly healing occurred. However, in patients from both trials with moderate to severe disease, dexlansoprazole MR 90 mg was superior to lansoprazole (83%–93% dexlansoprazole vs. 74%–87% lansoprazole; $p < 0.05$). All treatment groups in both trials were very effective in maintaining heartburn free days with median percentages of 82.1%–83.0% (study1–study 2) dexlansoprazole MR 60 mg, 84.2%–80.8% dexlansoprazole MR 90 mg and 80.0%–78.3% lansoprazole 30 mg. All regimens in both studies were equally effective in relieving nighttime symptoms and the median number of rescue medication days was similar between treatment groups.

It should be noted that only the 60 mg dexlansoprazole MR dose has been approved by US FDA for healing EE.

Non-erosive reflux disease

Patients with symptoms of GERD but no endoscopic evidence of EE have non-erosive reflux disease (NERD). Due to poorly understood physiologic

Table 4. Summary of efficacy and maintenance of healing clinical trials of dexlansoprazole MR.^{28,29,33,34}

Study	Indication	Design and enrollment criteria	N	Setting	Assessment	Results
Metz et al ³³	Relapse prevention in healed erosive esophagitis	6-month, randomized double-blind, adult (≥ 18 years) patients with healed EE; DMR 30 mg, 60 mg, or placebo	445	75 US and 19 non-US centers	Endoscopy at 1, 3, and 6 months; Severity of heartburn (5-point scale); Quality of life assessment	DMR 30 mg and 60 mg were superior to placebo (75%, 83% and 27, p < 0.0025); DMR demonstrated heartburn free days (91%–96%) and heartburn-free nights (96%–99%)
Howeden et al ²⁹	Maintenance of healing in erosive esophagitis	6-month, randomized, adult (≥ 18 years) patients with healed EE; DMR 60 or 90 mg or placebo	451	105 US centers	Endoscopy at 1, 3, and 6 months; Severity of heartburn (5-point scale); Quality of life assessment	DMR 60 mg and 90 mg were superior to placebo (87%, 82% and 26%; p < 0.0025) life table and (66%, 65%, and 14%) (crude rate). 24-hour heartburn free days (60 mg, 96%; 90 mg, 94%; placebo, 19%) and nights (60 mg, 98%; 90 mg, 97%; placebo, 50%)
Fass et al ³⁴	Day and nighttime heartburn in non-erosive reflux disease	4-week, randomized, double-blind, adult (≥ 18 years) patients with NERD; DMR 30 mg, 60 mg, or placebo	947	154 US centers	% of 24-hour heartburn-free days (primary) and nights without heartburn (secondary); quality of life and symptom severity questionnaires	DMR had greater median % 24-hour heartburn free days [54.9% (30 mg), 50% (60 mg), 17.5% (placebo)]; p < 0.00001; DMR reduced symptom severity and improved quality of life
Sharma et al ²⁸ (two clinical trials reported in same publication)	Erosive esophagitis healing	8-week, double-blind, randomized, endoscopically confirmed EE, adults (≥ 18 years), HP-; DMR 60 mg or 90 mg or lansoprazole 30 mg	2038 and 2054 patients	188 US and 118 non-US centers	% of patients with complete healing at 8 weeks (primary); % healing at 4-weeks, C and D patients % healing at 8-weeks (secondary)	DMR achieved non-inferiority to lansoprazole. DMR healed 92%–95% vs. 86%–92% for lansoprazole; p > 0.025). Week 4 healing was >64% with all treatment in both studies. In moderate to severe EE, DMR 90 mg was superior to lansoprazole

Abbreviations: N, number of patients; DMR, dexlansoprazole MR; EE, erosive esophagitis; NERD, non-erosive reflux disease; HP, *Helicobacter pylori* negative.



differences between NERD compared to other forms of reflux disease, patients have lower symptom response rates to therapy than do patients with EE. The NERD populations is heterogeneous in that some patient's symptoms are related to abnormal esophageal acid reflux while others are have a hypersensitivity of acid even with normal acid exposure. Dexlansoprazole MR has been evaluated in one study in patients with NERD.³⁴ A total of 947 patients with endoscopic negative reflux disease were randomized to receive dexlansoprazole MR 30 mg or 60 mg or placebo daily for 4 weeks. Patients were enrolled in this double blind trial regardless of their *Helicobacter pylori* (HP) status. The primary efficacy endpoint was the percentage of 24-hour heartburn-free days assessed by a patient kept daily diary. Secondary efficacy endpoints were the percentage of days without heartburn and the percentage of nights without heartburn. In addition, safety was assessed in all patients. Patient's demographics were similar among all groups in reference to gender, ethnicity and age. Patients' were generally overweight with a body mass index (BMI) > 29 in all groups and positive HP status was observed in 28.1% to 30.2% of (mean for all patient 28.9%) patients. The percentage of 24 hour heartburn-free days was significantly greater in both dexlansoprazole MR 30 mg and 60 mg groups compared with the placebo group (54.9% vs. 50% vs. 18.5% respectively; $p < 0.00001$). The percentage of nights patients were heartburn free was significantly better in both dexlansoprazole MR 30 mg (80.8%) and 60 mg (76.9%) compared to the placebo group (51.7%; $p < 0.00001$). All additional efficacy endpoints followed a similar pattern favoring both dexlansoprazole MR groups.

Adverse events (AEs) were similar between the two dexlansoprazole MR and placebo treatment groups with an incidence of 35%, 32% and 32%, respectively. Diarrhea, headache, nausea and vomiting were the most frequent AEs reported. This trial demonstrated that dexlansoprazole MR was superior to no treatment (placebo) in the management of symptoms related to non-erosive reflux disease.

Maintenance of healing in healed erosive esophagitis

Most patients whose EE is initially healed will relapse within a 12 month post-treatment period.⁴ Therefore, long term acid-suppression, usually with a PPI is recommend to maintain healing, maintain symptom

control, prevent complications and maintain quality of life consistent with end of treatment of the EE.^{4,33,35} Two published trials employing similar study designs evaluated the effectiveness of dexlansoprazole MR in maintaining healed EE and continue symptom relief.^{29,33} The first of the two trials evaluated dexlansoprazole MR 30 mg and 60 mg or placebo once daily for 6 months in patients with healed EE.²⁹ The trials primary endpoints included the percentage of patients who maintained endoscopic healing over the 6 month treatment and continued symptom relief based on patient daily diaries. Both dexlansoprazole MR 30 mg (75%) and 60 mg (83%) were superior to placebo (27%; $p < 0.0025$) by life-table analysis for maintaining healed EE. Crude maintenance rates were slightly lower at 66% for both dexlansoprazole MR groups and 14% for placebo. Dexlansoprazole MR had a greater percentage of heartburn-free days (91%–96%) and heartburn-free nights (96%–99%) than placebo (29%–72%). In a sub-analysis of patients with LA C and D EE at baseline, dexlansoprazole MR 60 mg was more effective in maintaining healing to a greater extent than the 30 mg group (85% vs. 63%; $p = 0.03936$). However, the total number of patient's was small and therefore the values did not reach stastical significance. Adverse events were similar between the two dexlansoprazole MR groups and placebo except for a higher incidence of upper respiratory tract infection and higher gastrin levels in those patients receiving the PPI.

The second study was similar in all aspects except patients were randomly assigned to receive dexlansoprazole MR 60 mg or 90 mg or placebo.³³ The trial was double-blind and patients were evaluated over a 6 month treatment period. Consistent with the previous study, dexlansoprazole MR 60 mg and 90 mg were more effective than placebo in maintaining healing (87%, 82%, 26%, respectively; $p < 0.0025$). Heartburn free days (60 mg 96%, 90 mg 94%, placebo 19%) and nights (60 mg 98%, 90 mg 97%, placebo 50%) again followed similar patterns with both doses of dexlansoprazole MR being superior to placebo. Adverse events were similar between placebo and dexlansoprazole MR groups with gastrointestinal side effects being the most commonly reported. In contrast to the first reported maintaince trial, the placebo group had a stastitcally higher incidence of upper respiratory tract infections than either dexlansoprazole MR treatment group.



Place in Therapy and Patient Preference

PPIs are highly effective in the treatment of GERD and EE and for maintaining healing in patients with treated EE. All marketed PPIs have been proven effective, but yet unmet needs for patients still exist. The need for a rapid onset agent for prompt symptom relief is of importance as is the need for an agent to be taken on-demand regardless of timing with a meal. The failure of current PPIs to provide complete-sustained symptom relief is also an important concern. The benchmark for effectiveness of a PPI has been the percentage of time over a 24-hour period the pH > 4 is maintained. Dexlansoprazole MR's dual release mechanism increases and prolongs the serum concentration that in turn allows for sustained gastric pH > 4. It appears that dexlansoprazole MR, like other PPIs is equivalent in healing and symptom rate control for patients with mild to moderate EE (LA grades A and B), but is more effective than lansoprazole in moderate to severe EE (LA grades C and D) which would be consistent with a greater duration of acid suppression. Whether dexlansoprazole MR proves to be superior to other PPIs that suppress gastric pH for prolonged periods (e.g. esomeprazole) remains to be seen as head-to-head clinical trials have not been conducted.

However, dexlansoprazole MR does allow the patient to dose the drug regardless of meals and at bedtime if desired and still achieve prolonged pH control. This feature has not been demonstrated or well studied for other PPIs (exception omeprazole IR in sodium bicarbonate) and offers a distinct advantage of dexlansoprazole MR over other DR PPIs. Allowing patients to dose dexlansoprazole MR as desired, may improve compliance, result in potentially greater healing rates, and increase overall symptom control.

Conclusions

Dexlansoprazole MR is a novel dual release PPI that results in prolonged serum concentrations and extensive acid suppression. It is available as 30 mg and 60 mg capsules and is indicated in erosive esophagitis, maintenance of erosive esophagitis healing, and relief of symptomatic non-erosive reflux disease. In comparative clinical trials, dexlansoprazole MR was similar to lansoprazole in rates of erosive esophagitis healing and maintenance of healing in long term therapy. However, in those patients with moderate to severe disease,

improvements in healing and symptom relief were higher with dexlansoprazole MR. The safety profile was favorable and similar to lansoprazole in the comparative clinical trials. Because of the extensive acid suppression and the ability to take dexlansoprazole MR without regard to food or time of day makes this product an attractive option for some patients. The potential benefits and risks of dexlansoprazole MR need to be evaluated with further clinical investigations.

Disclosure

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