Proton pump inhibitors for the treatment of patients with erosive esophagitis and gastroesophageal reflux disease: current evidence and safety of dexlansoprazole

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Abstract: Gastroesophageal reflux disease is the most common upper gastrointestinal disorder in the US. It is associated with a variety of complications and significantly impacts quality of life. Proton pump inhibitors are the most effective treatment. Dexlansoprazole modified release (MR) is a proton pump inhibitor that employs a novel release formulation that prolongs its absorption and allows for more flexibility in dosing. Dexlansoprazole MR can be dosed without regard to food intake or time of day, and once-daily dosing may replace twice-daily dosing of other agents. Dexlansoprazole MR is effective for healing and maintenance of erosive esophagitis, and for the treatment of nonerosive disease, including nocturnal gastroesophageal reflux disease. Dexlansoprazole MR is safe and well tolerated, and can improve quality of life.

Keywords: dexlansoprazole, proton pump inhibitors, gastroesophageal reflux disease, erosive esophagitis

Introduction

Gastroesophageal reflux disease (GERD) is the most common upper gastrointestinal disorder in the US and is estimated to affect 18.6 million people. 1 The prevalence of GERD in the Western world is 10%–20%, with 20% of the US adult population experiencing symptoms weekly and 7% daily. 1-3 The incidence of GERD and its complications, including erosive esophagitis (EE), esophageal strictures, Barrett’s esophagus, and even esophageal adenocarcinoma, has been increasing over the last 2 decades. 4 GERD is associated with 50% of noncardiac chest pain, 5 78% of chronic hoarseness, 6 and 82% of asthma symptoms. 7 Approximately 30% of patients with GERD have EE, while the remainder have nonerosive reflux disease (NERD). 8

GERD has a significant impact on quality of life, particularly in the elderly, with patients experiencing pain as well as deficits in psychological, social, and physical functioning. 9,10 GERD also presents a significant economic burden, as an estimated 9.3 billion dollars is spent annually in the US on diagnosing and treating GERD and its complications. 10

Treatment goals for GERD are to eliminate symptoms, manage and prevent complications, maintain remission, and improve quality of life. 10 Although the initial therapy should focus on lifestyle modifications, the mainstay of treatment is acid suppression. Proton pump inhibitors (PPIs) are the most effective medical therapeutic agents for the treatment of GERD. 10
**PPIs: general considerations**

PPIs are currently the most effective treatment for GERD and its complications. This class of drugs irreversibly blocks the H⁺/K⁺-ATPase proton pumps in the parietal cells, the final common pathway of acid secretion. By undergoing acid-activation to sulfenamides, PPIs covalently bond to cysteine residues on the luminal surface of the proton pump, blocking ion transport and acid secretion. Chemically, all PPIs consist of a benzimidazole ring and a pyridine ring but vary in side ring substitution and have pKi's that range from 3.9 to 5.8.

PPIs have revolutionized the treatment of esophageal inflammation and GERD-related symptoms through potent and sustained inhibition of nocturnal and daytime food-stimulated acid secretion. Multiple studies have shown that PPIs provide more effective treatment and faster symptom relief than histamine H₂-receptor antagonists. This results from the longer and more potent acid suppression conferred by inhibition of the proton pump. PPIs are also superior to other drug therapies in preventing esophageal and extraesophageal symptoms, and in relieving reflux symptoms and nocturnal heartburn. PPIs are especially useful in the elderly, who often experience more severe disease and complications, and therefore require increased acid suppression. PPIs are more consistently effective for EE than for NERD, as this represents a heterogeneous disorder with a wide spectrum of esophageal acid exposure, resulting in variable symptom response.

There are six available PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, and dexlansoprazole) that range in cost, pharmacokinetics, and bioavailability but generally do not differ significantly in their relief of GERD symptoms. PPIs only inhibit active pumps, and therefore, the majority should be taken 30–60 minutes prior to food consumption, which is the primary stimulus for pump activation. When PPIs are dosed once daily, they should be given before the first meal of the day, as the amount of H⁺/K⁺-ATPase present in the parietal cell is greatest after a prolonged fast. If necessary for symptom control, a second dose can be administered before the evening meal. The importance of this dosing schedule has been seen in several studies.

**Limitations of PPIs**

Although PPIs are the most effective medical therapy for treating GERD and its complications, a significant number of patients, particularly those with NERD, have refractory symptoms on once-daily dosing. Approximately 10%–15% of adult patients with EE do not achieve full remission after 8 weeks of treatment and up to 40% of patients with NERD remain symptomatic on standard therapy. Relapse has been shown to occur within 6 months of initiating treatment in 15%–23% of adult patients with Los Angeles (LA) grades A and B, and 24%–41% with grades C and D. A recent meta-analysis found that reflux symptoms are not sufficiently controlled after the first dose of a PPI in two-thirds of patients, and nearly 50% of patients are symptomatic after 3 days. PPIs are also less effective for controlling nocturnal GERD. Many patients discontinue PPIs when their symptoms resolve, as demonstrated by a large population-based survey that found that only 55% of patients took a PPI once-daily for 4 weeks as prescribed, with 37% taking it for 12 or fewer days out of the month. Other factors affecting compliance include age, personality, knowledge about the disorder being treated, side effects, number of pills per day, socioeconomic status, and insurance coverage. Dosing time is another critical factor underlying failure of PPIs, as most must be taken 30–60 minutes before a meal in order to achieve maximal efficacy. In one study of refractory GERD symptoms, it was found that only 46% of patients dosed optimally. A survey similarly revealed nighttime dosing in 52% of patients. Noncompliance with dosing time likely results from both patient preference and misinformation about administration, as one national survey showed that 36% of physicians give their patients no directions or incorrect directions regarding mealtime dosing of PPIs, 26% give no instructions or say that timing is unimportant, and 10% incorrectly advise their patients to take them with or after food.

Even with appropriate, once-daily dosing, PPIs are estimated to inhibit only 70% of active proton pumps. Proton pumps are active at different times, and –25% are regenerated daily, with significant variation in turnover rate. The short half-life of PPIs (1–2 hours) prevents 24-hour control of gastric acid, which continues to be secreted by pumps that are uninhibited or regenerated. Increasing the once-daily dose of PPIs has shown only marginal benefit and does not increase the duration of acid control. Twice-daily PPI administration,
either by splitting or doubling the dose, is reported to improve acid control\textsuperscript{34} but is associated with poorer compliance.

There are many factors that contribute to persistent symptoms with PPI therapy. These include less acidic or nonacidic reflux such as bile reflux, esophageal hypersensitivity, nocturnal acid breakthrough, psychological comorbidity, eosinophilic esophagitis, gastroparesis, and irritable bowel syndrome.\textsuperscript{39} Reduced PPI bioavailability, PPI resistance, \textit{Helicobacter pylori} status, and rapid PPI metabolism as a result of mutations in the 2C19 isoform of cytochrome p450 are possible but less likely causes of PPI failure.\textsuperscript{39}

While they have an excellent safety profile,\textsuperscript{23} the most common side effects of PPIs are abdominal pain, nausea, headache, pharyngitis, and diarrhea.\textsuperscript{8} Long-term use has been associated with a variety of adverse effects (Table 1). PPI use has been linked to decreased absorption of magnesium, vitamin B12, and iron.\textsuperscript{40} PPIs have also been linked to reduced calcium absorption and subsequent development or exacerbation of osteoporosis and bone fracture.\textsuperscript{19} Several studies have found an association between long-term PPI use and hip fractures, although a recent case–control study showed that this occurs in patients who are receiving higher doses of PPIs and have at least one additional risk factor.\textsuperscript{41}

Another important adverse effect associated with long-term PPI use is bacterial proliferation through increased gastric pH that leads to gut microflora overgrowth, and bacterial translocation, as well as immunomodulatory and anti-inflammatory effects. As demonstrated by several studies, these changes can increase susceptibility to overgrowth of enteric bacterial pathogens, such as \textit{Clostridium difficile}.\textsuperscript{42} Data on recurrent \textit{C. difficile} infection with PPI use are mixed.\textsuperscript{43,44} PPI-induced bacterial proliferation has also been associated with an increased incidence of community-acquired pneumonia.\textsuperscript{10,45}

PPIs may also be associated with an elevated risk of myocardial infarction (MI). PPIs may have an indirect interaction with vascular function through alteration in nitric oxide synthesis.\textsuperscript{46} In patients with a history of MI, PPIs may also reduce the efficacy of clopidogrel.\textsuperscript{47} However, clinical data on PPI-associated MI are mixed, with large, observational studies and a few randomized controlled trials showing variable cardiovascular outcomes.\textsuperscript{48}

Recent literature suggests a correlation between PPI use and dementia.\textsuperscript{49,50} The mechanism by which PPIs are linked to dementia is unknown, although in both a cell model and mice, PPIs have been shown to increase levels of amyloid-beta peptides, which are the main component of amyloid plaques in Alzheimer’s dementia.\textsuperscript{51}

PPI use may be a risk factor for chronic kidney disease (CKD), potentially mediated by acute kidney injury or hypomagnesemia.\textsuperscript{52–54} In one study, PPIs were independently associated with a 20%–50% higher risk of CKD and acute kidney injury.\textsuperscript{55} While considering possible adverse events associated with long-term PPI use, it is important to note that the existing data on chronic acid suppression primarily come from observational, population-based studies that are susceptible to bias and various confounding factors.\textsuperscript{56} Therefore, while PPIs should only be prescribed for an appropriate clinical indication, they should not be withheld because of concerns about long-term effects.

Finally, long-term use of PPIs, like all gastric acid ant secretery drugs, increases release of gastrin by stimulation and hyperplasia of enterochromaffin-like (ECL) cells, particularly in patients with \textit{H. pylori} infection. Although hypergastrinemia alone has not been shown to cause carcinoid formation in humans, its lifelong impact on ECL cells is unknown.\textsuperscript{6} Hypergastrinemia may also be implicated in rebound acid hypersecretion (RAHS) following withdrawal of PPI therapy.\textsuperscript{57} Although RAHS may theoretically cause an exacerbation of GERD symptoms following PPI discontinuation, thereby leading to long-term PPI use, recent studies have found no evidence of symptomatic RAHS in patients with reflux disease.\textsuperscript{57}

### Table 1 Adverse effects of long-term PPI use

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Reduced vitamin and mineral absorption</td>
</tr>
<tr>
<td>Iron</td>
</tr>
<tr>
<td>Calcium</td>
</tr>
<tr>
<td>Magnesium</td>
</tr>
<tr>
<td>B12</td>
</tr>
<tr>
<td>Infections due to bacterial proliferation</td>
</tr>
<tr>
<td>\textit{Clostridium difficile}</td>
</tr>
<tr>
<td>Community-acquired pneumonia</td>
</tr>
<tr>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Alteration in pH-dependent drug pharmacokinetics</td>
</tr>
<tr>
<td>Antibiotics</td>
</tr>
<tr>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Decreased efficacy of clopidogrel</td>
</tr>
<tr>
<td>Dementia</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
</tr>
</tbody>
</table>

**Abbreviation:** PPI, proton pump inhibitor.

**Dexlansoprazole modified release**

Dexlansoprazole (Figure 1) is the newest PPI and has been available in the US for the treatment of acid-related disorders since 2009.\textsuperscript{20} Dexlansoprazole is the \textit{R}-enantiomer of its racemic parent, lansoprazole, and was initially chosen for further clinical development because it constitutes >80% of circulating drug and is associated with slower hepatic clear-
ance and greater systemic exposure than the S-enantiomer.\textsuperscript{58} The commercially available form, dexlansoprazole modified release (MR), is a modified-release formulation that was designed to address the pharmacodynamic and pharmacokinetic limitations of PPIs which give rise to breakthrough symptoms and necessitate pre-mealtime dosing. Compared with conventional PPIs, dexlansoprazole MR has improved bioavailability and metabolism, and more efficiently inhibits proton pumps in the gastric mucosa.\textsuperscript{20} Dexlansoprazole MR is indicated for the treatment of symptomatic nonerosive GERD, healing of EE, and maintenance of healing of EE.\textsuperscript{59}

Properties of dexlansoprazole MR

Dexlansoprazole MR uses a novel dual-delayed-release (DDR) formulation that delivers the drug in two phases, thereby inhibiting newly activated proton pumps that regenerate after initial PPI inactivation.\textsuperscript{60} The dexlansoprazole MR capsule contains two distinct types of enteric-coated granules: the first, which makes up one-quarter of the granules, is released at a pH of 5.5 in the proximal duodenum 1–2 hours after ingestion, while the second is released at a pH of 6.8 in the distal small bowel 4–5 hours after ingestion (Figure 2).\textsuperscript{61} As a result of this dual-peak profile,\textsuperscript{62} dexlansoprazole prolongs acid suppression and produces the greatest inhibitory effects on proton pumps of all PPIs.\textsuperscript{61} The DDR technology also increases the drug’s mean plasma residence time, or the average time a drug molecule spends in systemic circulation. In a prospective, randomized study comparing the pharmacokinetics of dexlansoprazole MR with lansoprazole, the mean plasma residence time and area under the curve (AUC) of dexlansoprazole MR were significantly higher (Table 2).\textsuperscript{63} The delivery system, as opposed to delayed hepatic elimination, is primarily responsible for the drug’s prolonged plasma residence time, as the elimination half-life of dexlansoprazole MR is similar to that of other PPIs.\textsuperscript{64}

Several studies have demonstrated the effect of the DDR formulation on acid suppression. In one crossover study comparing single-dose dexlansoprazole MR 60 mg and esomeprazole 40 mg, 24-hour intragastric pH for dexlansoprazole MR was higher, particularly in the second part of the day.\textsuperscript{65} Another trial comparing three different doses of dexlansoprazole MR (60, 90, and 120 mg) with lansoprazole 30 mg found that mean AUC and $C_{\text{max}}$ values for dexlansoprazole MR were 3–7 and 1.5–3 times higher, respectively, and duration of drug exposure was extended, as evidenced by a prolonged duration of maximum serum concentration ($t_{\text{max}}$) and substantially higher plasma concentrations 3–8 hours post-dose.\textsuperscript{60}

Administration

While conventional PPIs are recommended to be taken 30–60 minutes prior to the morning meal,\textsuperscript{62} dexlansoprazole, with its prolonged duration of action, has a more flexible

Figure 1

Chemical structure of dexlansoprazole.

Note: The chemical name of dexlansoprazole is (+)-2-[(R)-\{(3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl}sulfinyl]-1H-benzimidazole. Its empirical formula is C\textsubscript{16}H\textsubscript{14}F\textsubscript{3}N\textsubscript{3}O\textsubscript{2}S, and it has a molecular weight of 369.36 Da.\textsuperscript{68}

Figure 2

Mean plasma concentration–time following oral administration of different doses of dexlansoprazole MR.

Note: Reproduced with permission. Metz DC, Vakily M, Dixit T, Mulford D. Review article: dual delayed release formulation of dexlansoprazole MR, a novel approach to overcome the limitations of conventional single release proton pump inhibitor therapy. Aliment Pharmacol Ther. Wiley & Sons ©2009 Takeda Global Research & Development Center, Inc.60

Abbreviation: MR, modified release.
dosing schedule. The efficacy of dexlansoprazole MR regardless of food intake was demonstrated in one crossover study of 48 healthy volunteers who took dexlansoprazole MR under four conditions: during a fast, 30 or 5 minutes prior to a meal, or 30 minutes after a meal. Among the groups, no significant differences were found in $C_{\text{max}}$ or 24-hour intragastric pH (Table 3), suggesting that food and timing of dose did not affect acid suppression.66

Dexlansoprazole can also be administered at any time of day, as evidenced by a study in which it was taken 30 minutes prior to breakfast, lunch, dinner, or an evening snack. Intragastric pH $>4$ for each group was 71%, 74%, 70%, and 64%, respectively, with the only statistically significant difference occurring between the breakfast and evening snack groups. There was also a small increase in pH of 0.2 between lunch and breakfast groups. While statistically significant, these differences did not appear to have any impact on clinical outcomes.67

Table 2 Pharmacokinetics of dexlansoprazole MR and lansoprazole following 5 days of once-daily administration

<table>
<thead>
<tr>
<th>PPI agent</th>
<th>$C_{\text{max}}$ (ng/mL)</th>
<th>AUC24 (ng·h/mL)</th>
<th>AUC24 (ng·h/mL)</th>
<th>MRT (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexlansoprazole 60 mg</td>
<td>1,434 (703)</td>
<td>6,737 (4,708)</td>
<td>6,720 (4,906)</td>
<td>5.56 (1.78)</td>
</tr>
<tr>
<td>Dexlansoprazole 30 mg</td>
<td>658 (263)</td>
<td>3,182 (1,559)</td>
<td>3,275 (1,539)</td>
<td>5.65 (1.53)</td>
</tr>
<tr>
<td>Lansoprazole 30 mg</td>
<td>845 (380)</td>
<td>1,886 (1,547)</td>
<td>1,949 (1,949)</td>
<td>2.83 (2.58)</td>
</tr>
</tbody>
</table>

Notes: Data are presented as mean (standard deviation). Data from Vakily et al.63

Abbreviations: MR, modified release; $C_{\text{max}}$, maximum plasma concentration; AUC, area under the plasma concentration–time curve from time zero to last measurable concentration; AUC24, AUC from time zero to 24 hours; MRT, mean residence time; PPI, proton pump inhibitor.

Table 3 Pharmacokinetic and pharmacodynamic parameters following a single dose of 90 mg dexlansoprazole MR under various conditions

<table>
<thead>
<tr>
<th>Dosing interval</th>
<th>$C_{\text{max}}$ (ng/mL)</th>
<th>AUC (ng·h/mL)</th>
<th>Mean intragastric pH</th>
<th>Percentage of time with intragastric pH $&gt;4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>1,486</td>
<td>7,058</td>
<td>4.46</td>
<td>64</td>
</tr>
<tr>
<td>30 minutes before breakfast</td>
<td>1,597</td>
<td>7,970</td>
<td>4.53</td>
<td>66</td>
</tr>
<tr>
<td>5 minutes before breakfast</td>
<td>1,653</td>
<td>8,198</td>
<td>4.43</td>
<td>62</td>
</tr>
<tr>
<td>30 minutes after breakfast</td>
<td>1,825</td>
<td>8,157</td>
<td>4.25</td>
<td>57</td>
</tr>
</tbody>
</table>

Note: Data from Lee et al.66

Abbreviations: MR, modified release; $C_{\text{max}}$, maximum plasma concentration; AUC, area under the plasma concentration–time curve.

Dexlansoprazole delayed-release orally disintegrating tablet

Dexlansoprazole is also available as an orally disintegrating tablet that dissolves on the tongue and is swallowed without water.69 It may be of benefit to patients who are unable or unwilling to swallow pills. The disintegrating tablet contains the same two types of granules found in dexlansoprazole MR and therefore follows the same DDR pattern as well as has equivalent absorption, bioavailability, and acid suppression.70

While the package insert recommends dosing 30 minutes prior to meal,69 a study of healthy volunteers who took the disintegrating tablets after a fast or 30 minutes after a meal found no significant difference in $C_{\text{max}}$ or AUC.71 Additionally, no significant difference in bioavailability was found when the disintegrating tablet was allowed to dissolve, was swallowed with water, or was swallowed whole.72

Efficacy of dexlansoprazole MR

Erosive esophagitis

The efficacy of dexlansoprazole MR in healing EE was demonstrated in two identical, double-blind, placebo-controlled studies in which 4,092 patients with EE were randomized to receive lansoprazole 30 mg, dexlansoprazole MR 60 mg, or dexlansoprazole MR 90 mg daily. Complete healing at 8 weeks was found in 92%–93% of the dexlansoprazole MR 60 mg group, 93%–95% of the 90 mg group, and 86%–92% of the lansoprazole group. While this difference was not statistically significant, it demonstrated that dexlansoprazole MR was non-inferior to lansoprazole. A subgroup analysis of patients with severe EE, of LA grades C and D, showed that dexlansoprazole MR 90 mg was superior to lansoprazole.
with a 7%–8% higher healing rate (Table 4). No significant difference was found between the three treatment groups in control of both daytime and nighttime heartburn symptoms. In a further study that grouped patients by body mass index, dexlansoprazole MR 60 mg was associated with superior healing of EE as compared to lansoprazole in patients with body mass index >30 kg/m².74

Dexlansoprazole MR is also effective for the maintenance of healing of EE. In a 6-month follow-up of the trial mentioned, patients whose EE had been successfully healed were randomized to one of three groups: placebo or dexlansoprazole MR 30 or 60 mg. Healing was maintained in 72.7% of the placebo group, 74.9% of the dexlansoprazole MR 30 mg group, and 82.5% of the dexlansoprazole MR 60 mg group. While both doses of dexlansoprazole MR were superior to placebo, the difference between them was not statically significant. However, when limited to patients with severe EE, of LA grades C and D, the 60 mg dosage was found to be superior with maintenance of healing of 85% compared to 63% for the 30 mg dosage.75

Nonerosive reflux disease
Dexlansoprazole MR is also effective in patients with NERD. In a 1-month study by Fass et al76 of patients experiencing symptoms at least 4 days per week, dexlansoprazole MR was superior to placebo in producing symptom-free, 24-hour periods (Table 5). Additionally, the mean severity of heartburn symptoms was reduced in patients who received dexlansoprazole MR compared with placebo. For all studied efficacy outcomes, no statistical difference was found between dexlansoprazole MR 30 and 60 mg.76

### Table 4 Percent of patients with healed Los Angeles grade C or D erosive esophagitis at 8 weeks (life table analysis)

<table>
<thead>
<tr>
<th>PPI agent</th>
<th>Life table analysis</th>
<th>Crude rate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexlansoprazole 60 mg</td>
<td>88.2</td>
<td>78.7</td>
</tr>
<tr>
<td>Dexlansoprazole 90 mg</td>
<td>88.9</td>
<td>80.1</td>
</tr>
<tr>
<td>Lansoprazole 30 mg</td>
<td>81.5</td>
<td>71.8</td>
</tr>
</tbody>
</table>

Note: Data from Sharma et al.73
Abbreviation: PPI, proton pump inhibitor.

### Table 5 Percentage of 24-hour heartburn-free days and nights during maintenance treatment of healed erosive esophagitis

<table>
<thead>
<tr>
<th>PPI agent</th>
<th>Percentage of heartburn-free days</th>
<th>Percentage of heartburn-free nights</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexlansoprazole 60 mg</td>
<td>50</td>
<td>76.9</td>
</tr>
<tr>
<td>Dexlansoprazole 30 mg</td>
<td>54.9</td>
<td>80.8</td>
</tr>
<tr>
<td>Placebo</td>
<td>18.5</td>
<td>51.7</td>
</tr>
</tbody>
</table>

Note: Data from Fass et al.76
Abbreviation: PPI, proton pump inhibitor.

### Nighttime GERD
Dexlansoprazole MR is superior to placebo for the treatment of nighttime GERD, as demonstrated in the study by Fass et al.76 Additionally, in a 4-week trial of 305 patients with moderate-to-very severe nocturnal heartburn and sleep disturbance, dexlansoprazole MR 30 mg, compared with placebo, significantly increased the percentage of nights without nocturnal GERD from 35.7% to 73.1% and was superior in reducing nighttime symptoms and sleep disturbance.77

### Comparison with other PPIs
Lansoprazole is the only PPI to which dexlansoprazole MR has been directly compared.62,74 There is one indirect comparison in which data from multiple randomized controlled trials were pooled and analyzed. Dexlansoprazole MR 30 mg resulted in superior control of GERD symptoms compared to esomeprazole 20 or 40 mg. However, no difference in healing or maintenance of healing in EE was found. No comparison of symptom control in EE could be made because of differences in the definitions used in the included trials.64

### Quality of life
Several studies have shown that effective treatment of GERD can lead to a significant increase in health-related quality of life.78,79 It is therefore no surprise that the treatment of NERD with dexlansoprazole MR leads to significant improvements in health-related quality of life, including sleep quality, work productivity, work attendance, and less impairment of regular activities.77 In addition to showing improvement over placebo, dexlansoprazole MR also leads to increased quality of life compared to other PPIs. In one study in which patients with controlled GERD on twice-daily PPIs were transitioned to dexlansoprazole MR, the patients whose symptoms continued to be well controlled had a statistically significant increase in quality-of-life scores.68

### Safety
### Drug interactions
All PPIs, including dexlansoprazole MR, undergo extensive hepatic metabolism via cytochrome P450 through hydroxylation by CYP2C19, and less prominently, through oxidation by CYP3A4.80 Certain patients are poor metabolizers of PPIs as a result of a mutation that decreases production of CYP2C19.81

In vitro studies indicate that dexlansoprazole has the potential to inhibit CYP2C19 and CYP3A4, and may also induce hepatic CYP1A and CYP2C9 activity.61 However, the only in vivo drug interaction study of dexlansoprazole...
MR found that coadministration with warfarin, diazepam, phenytoin, or theophylline did not affect the pharmacokinetics of these drugs. Additionally, coadministration with warfarin did not affect the international normalized ratio.\textsuperscript{52} Dexlansoprazole MR is therefore unlikely to alter the pharmacokinetic profile of other drugs that are metabolized by CYP2C19, CYP2C9, CYP1A2, and CYP3A.\textsuperscript{85} However, for drugs with a narrow therapeutic window, caution and frequent monitoring are advisable.

Recently, there has been growing concern about the propensity of PPIs to decrease the antiplatelet activity of clopidogrel, which is often coadministered with PPIs to reduce risk of gastrointestinal bleeding.\textsuperscript{83} PPI metabolism and clopidogrel activation both involve CYP2C19,\textsuperscript{84,85} potentially leading to decreased clopidogrel activity.\textsuperscript{86} Observational studies and retrospective reviews have mixed findings on whether this pharmacokinetic interaction leads to increased clinical risk of cardiovascular events.\textsuperscript{83} In one prospective study that examined the pharmacokinetic and pharmacodynamic effects of dexlansoprazole MR, lansoprazole, omeprazole, and esomeprazole on clopidogrel and its active metabolites, all PPIs decreased the $C_{\text{max}}$ of clopidogrel, but dexlansoprazole MR decreased it the least. Furthermore, the AUC of clopidogrel and its active metabolite was not affected by dexlansoprazole MR, and concomitant dosing did not significantly affect measures of platelet activation.\textsuperscript{87}

Like other PPIs, dexlansoprazole MR reduces the acid environment and may interfere with the absorption of drugs whose bioavailability depends on pH. The HIV drugs atazanavir and nelfinavir should not be coadministered with dexlansoprazole MR because of significant reduction in systemic exposure.\textsuperscript{20} Similarly, dexlansoprazole MR should also be avoided with ketoconazole, itraconazole, ampicillin, and erlotinib, as these medications rely on low pH values for absorption.\textsuperscript{61} Plasma concentration levels of digoxin and tacrolimus may increase when given with dexlansoprazole MR, and drug levels should be monitored closely. The risk of increased tacrolimus levels is particularly high in patients with moderate or slow CYP2C19 metabolism, as tacrolimus is a substrate for CYP3A4.\textsuperscript{20}

### Hypergastrinemia

Dexlansoprazole MR causes an increase in serum gastrin levels. In studies of the chronic use of dexlansoprazole MR, serum levels of gastrin more than double over the first 3 months and then reach a steady state. Interestingly, the elevation in serum gastrin levels is not dose dependent, and levels typically return to baseline with discontinuation. The increase in serum gastrin levels with dexlansoprazole MR, which is consistent with that of other PPIs, is a physiologic response to acid suppression and is not harmful in isolation.\textsuperscript{88,89} There might be concern that long-term elevation of gastrin levels associated with hyperplasia of the ECL cells would lead to sequelae such as ECL tumors and cancer.\textsuperscript{90} However, biopsies taken after 12 months of continuous dexlansoprazole MR use do not show hyperplasia of these cells or find any evidence of carcinoid tumors, gastric adenocarcinoma, or lymphoma.\textsuperscript{58,89} Another potential consequence of elevated gastrin levels is RAHS upon PPI discontinuation. However, a retrospective study examining EE patients who healed with dexlansoprazole MR and were then randomized to the placebo arm of the maintenance trial found no worsening of GERD symptoms upon dexlansoprazole MR discontinuation compared with baseline.\textsuperscript{91}

### Side effects

Dexlansoprazole MR has a low rate of side effects. The most common side effect is upper respiratory tract infection, with as many as 13%–14% of patients experiencing such symptoms. Upper respiratory tract infections are more common among patients on higher doses of dexlansoprazole MR and in patients with preexisting seasonal allergies.\textsuperscript{58,89} Other frequent side effects include abdominal pain, diarrhea, headache, nausea, abdominal bloating, flatulence, and constipation.\textsuperscript{20,89} One study found that side effects resulted in drug discontinuation in only 0.7% of cases.\textsuperscript{20} Data pooled from 4,270 patients in the six Phase III clinical trials of dexlansoprazole MR showed that there was a lower overall rate of treatment-related adverse events with dexlansoprazole MR than with lansoprazole or placebo. The incidence of severe adverse events was slightly higher in the dexlansoprazole MR group; however, this was not statistically significant.\textsuperscript{89} Additionally, even at doses of up to 300 mg, dexlansoprazole MR was not found to have any effect on the QT or QTc interval.\textsuperscript{20}

### Conclusion

GERD is the most common upper gastroenterology disorder in the US. Although PPIs are currently the most effective treatment for GERD and its complications, a significant number of patients, particularly those with NERD, have refractory symptoms on once-daily dosing. PPIs are also associated with several long-term adverse events, including decreased absorption of magnesium, vitamin B12, and iron, infections due to bacterial proliferation, dementia, and CKD. Dexlansoprazole MR, the newest PPI, was designed to address the pharmacodynamic and pharmacokinetic
limitations of other PPIs. Through a novel DDR formulation that prolongs its bioavailability, dexlansoprazole MR can be dosed without regard to food or time of day, improves control of nighttime symptoms, and may allow for once-daily dosing in more refractory cases. Dexlansoprazole MR has an excellent safety profile with minimal drug interactions, including clopidogrel. Dexlansoprazole MR is currently approved for the healing and maintenance of EE, and for relief of NERD symptoms.

**Disclosure**

The authors report no conflicts of interest in this work.

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