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Safety profile of dexlansoprazole MR, a proton pump inhibitor with a novel dual delayed release formulation: global clinical trial experience

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SUMMARY

Background
Dexlansoprazole MR is a dual delayed release formulation of dexlansoprazole, an enantiomer of lansoprazole.

Aim
To assess safety of dexlansoprazole MR in phase 3 clinical trials.

Methods
Data from 4270 patients receiving dexlansoprazole MR 30 mg (n = 455), 60 mg (n = 2311) or 90 mg (n = 1864); lansoprazole 30 mg (n = 1363); or placebo (n = 896) in six randomized controlled trials and a 12-month safety study were pooled. Safety was assessed via adverse events, vital signs, electrocardiograms, clinical laboratory results and gastric biopsies. Adverse events were summarized per 100 patient-months of exposure to account for imbalances in study drug exposure.

Results
The number of patients with ≥1 treatment-emergent adverse event per 100 patient-months was higher in placebo (24.49) and lansoprazole (21.06) groups than in any dexlansoprazole MR (15.64–18.75) group. Fewer patients receiving dexlansoprazole MR discontinued therapy because of an adverse event ($P \leq 0.05$ vs. placebo). Seven patients died of events considered unrelated to study drug. Mean serum gastrin rose in all groups except placebo; increases were not dose-related. No clinically concerning trends were seen in gastric biopsy results. Endocrine cell hyperplasia, dysplasia and neoplasia were not observed.

Conclusion
Dexlansoprazole MR 30–90 mg has a safety profile comparable to that of lansoprazole.

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INTRODUCTION

Proton pump inhibitors (PPIs) are widely used in the treatment of gastro-oesophageal reflux disease (GERD) and other acid-related disorders. Their safety profile is well established in studies evaluating more than a decade of continual PPI use.[1] Few safety concerns have arisen with lansoprazole, one of the currently marketed PPIs in the United States. Limited untoward effects have been seen with lansoprazole in clinical studies even when administered at high doses (>60 mg/day) for up to 13 years in patients with Zollinger–Ellison syndrome,[2–4] for 6 years in patients with erosive oesophagitis (EO)[5, 6] and for up to 4 years in patients with duodenal ulcer.[7]

Dexlansoprazole MR is a modified-release formulation of dexlansoprazole, an enantiomer of lansoprazole, which employs an innovative delivery system with Dual Delayed Release (DDR) technology designed to prolong the dexlansoprazole plasma concentration vs. time profile and provide extended duration of acid suppression with once-daily (QD) dosing. Dexlansoprazole MR is characterized by a plasma concentration vs. time profile with two distinct peaks. Dexlansoprazole MR releases drug substance over a longer period of time than conventional delayed-release PPIs.[8, 9] Although this necessitates a higher daily dose than conventional delayed-release PPIs, the result is an increase in area under the curve without a commensurate increase in maximum observed concentration. The extended pharmacokinetic profile of dexlansoprazole MR has been shown to decrease gastric acid output over a prolonged period and to maintain intragastric pH >4 for a significantly longer time over the 24-h postdose period than lansoprazole (71% and 70% respectively for dexlansoprazole MR 60 and 90 mg compared with 60% for lansoprazole 30 mg; $P < 0.05$).[10]

The safety profile of dexlansoprazole MR has been evaluated in nonclinical and early clinical studies. In animal studies, high doses of dexlansoprazole (≤50 mg/kg/day) did not show substantive differences in adverse effects from those seen with lansoprazole at the same doses.[11, 12] In phase 1 studies, single doses up to 300 mg[13–17] and multiple doses up to 120 mg[10, 18, 19] were evaluated. Only 1 serious adverse event (AE) was reported (perforated appendicitis) in phase 1 studies, which was assessed by the investigator to be unrelated to dexlansoprazole MR.[18]

The phase 3 clinical development programme for dexlansoprazole MR included six randomized, double-blind, controlled studies and one randomized, open-label, 12-month, long-term study. These studies showed that dexlansoprazole MR is effective in a wide variety of GERD-related disorders, including symptomatic non-erosive GERD, EO and maintenance of healed EO. Three doses of dexlansoprazole MR (30, 60 and 90 mg) were used in the phase 3 studies, with placebo or lansoprazole 30 mg as comparators. Since the completion of these trials, the US Food and Drug Administration has approved the use of dexlansoprazole MR 30 mg QD for up to 6 months for the maintenance of healed EO and for up to 4 weeks for symptomatic nonerosive GERD and dexlansoprazole MR 60 mg QD for up to 8 weeks for healing of EO.[20]

Here, we report the overall safety profile of dexlansoprazole MR based on pooled phase 3 data from these trials and by indication as applicable.

MATERIALS AND METHODS

Patient population

A total of 4270 patients received dexlansoprazole MR during 6 phase three double-blind studies and one open-label, long-term safety study (Table 1). Of the 6 phase three randomized, controlled studies, two assessed symptom relief in patients with symptomatic, nonerosive GERD,[21] two assessed healing in patients with EO[22] and two assessed maintenance of healing of EO in patients for whom EO was healed with dexlansoprazole MR or lansoprazole in the preceding trials.[23, 24] An interim analysis of the open-label long-term safety study included patients who completed a symptomatic GERD study.[25]

Table 2 summarizes the baseline demographic characteristics of all the patients treated in these trials, organized by treatment group (placebo, dexlansoprazole MR and lansoprazole, all administered QD). Among all patients in clinical studies who received dexlansoprazole MR, majority were women (54%) and white (85%), with a mean age of 48 years (range, 18–90 years); 23% were smokers and 56% consumed alcohol. Significant differences were observed between treatment groups for gender and smoking status. A higher percentage of female patients (66%) than male patients participated in the placebo group because more women than men participated in the placebo-controlled, symptomatic nonerosive GERD studies. The percentage of smokers varied from 19% to 25% among treatment groups. All subjects screened for the phase 3

Table 1. Summary of the dexlansoprazole MR Global Clinical Trial Programme

Study	Trials, *n*	Dexlansoprazole MR (*n*)	Control (*n*)	Trial length	Endpoints
Symptomatic GERD	2	30, 60, or 90 mg (1246)	Placebo (609)	4 weeks	Symptom relief in patients with symptomatic, endoscopically confirmed, non-erosive GERD; safety
EO healing	2	60 or 90 mg (2729)	Lansoprazole 30 mg (1363)	4 or 8 weeks, depending on when healing occurred	EO healing and relief of GERD-related symptoms; safety
Maintenance of healed EO	2	30, 60, or 90 mg (609)	Placebo (287)	6 months	Maintenance of healed EO in patients with endoscopically proven healed EO from healing trials; safety
Long-term safety*	1	60 or 90 mg (313)	None (open-label extension)	12 months	Safety in patients who completed 1 of the symptomatic GERD trials

EO, erosive oesophagitis; GERD, gastro-oesophageal reflux disease; MR, modified release.
* Data used are from an interim analysis of an ongoing 12-months study.

studies were tested for the presence of *Helicobacter pylori* and underwent an endoscopy to assess the presence of EO. Patients with symptomatic nonerosive GERD were eligible for the GERD studies regardless of *H. pylori* status; however, patients positive for *H. pylori* were excluded from the EO studies.

Treatment exposure

Patients treated in the phase 3 studies received dexlansoprazole MR QD in at least 1 of 3 doses [30 mg (n = 455), 60 mg (n = 2311), 90 mg (n = 1864)], lansoprazole 30 mg QD (n = 1363) or placebo QD (n = 896) and included 651 patients treated for ≥24 weeks and 203 patients treated for ≥48 weeks with dexlansoprazole MR. Of note, patients could be represented in more than one study (for example, a single patient could participate in one of the healing studies for dexlansoprazole MR and be randomized to a different dose group for a maintenance study). Table 3 summarizes duration and exposure to treatment in all phase 3 studies by study population.

Adverse event reporting

Treatment-emergent AEs were defined as any unfavourable, unintended, or untoward sign, symptom or disease temporally associated with study drug, regardless of whether they were considered related to the study drug.

All AEs that occurred after the first dose of study drug through 30 days after discontinuation of study drug were summarized. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 10.0, International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland) coding dictionary. AEs were categorized by high-level terms (HLTs) and preferred terms (PTs).

Treatment durations and dexlansoprazole MR doses and/or comparators differed among the phase 3 studies. Patients receiving placebo in the maintenance of healed EO studies had much higher rates of premature discontinuation because of relapse of EO, resulting in a shorter duration of drug exposure compared with the active treatment groups. To account for this imbalance in study drug exposure, AEs were summarized by incidence per 100 patient-months (PM) of exposure.

Serious AEs (SAEs) were defined as AEs that resulted in death, hospitalization or prolongation of stay,

Table 2. Demographic and baseline characteristics of dexlansoprazole MR patients in phase 3 trials

Variable	Treatment group: Placebo (n = 896)	Dexlansoprazole MR (n = 4270)	Lansoprazole (n = 1363)	P*
Gender, n (%)				
Men	302 (34)	1971 (46)	727 (53)	<0.001
Women	594 (66)	2299 (54)	636 (47)	
Mean age ± s.d., year	48.4 ± 13.67	47.8 ± 13.67	47.3 ± 13.69	0.167
Race, n (%)				
White	757 (84)	3634 (85)	1186 (87)	0.154
Black	94 (10)	325 (8)	59 (4)	
Other	42 (5)	301 (7)	114 (8)	
Missing	3 (<1)	10 (<1)	4 (<1)	
Mean BMI ± s.d., kg/m^2	29.7 ± 6.68	29.8 ± 6.45	29.9 ± 6.15	0.727
Alcohol users, n (%)	487 (54)	2399 (56)	752 (55)	0.563
Smokers, n (%)	172 (19)	969 (23)	340 (25)	0.006
Caffeine users, n (%)	703 (78)	3391 (79)	1085 (80)	0.756

BMI, body mass index; MR, modified release.
* P values are from chi-square tests for gender, race, alcohol use, smoking status and caffeine use and from a one-way analysis of variance with treatment as the factor for age and BMI. The test for race uses white vs. all other races combined.

Table 3. Overall extent of treatment exposure in phase 3 studies

	Treatment group: Placebo (n = 896)	Dexlansoprazole MR (n = 4270)	Lansoprazole* (n = 1363)
Treatment duration, weeks			
<4	248	667	187
4–<8	584	2169	788
8–<12	4	674	386
12–<24	21	109	2
24–<36	39	426	0
36–<48	0	22	0
≥48	0	203	0
Mean ± s.d. days on treatment			
All phase 3 studies	35.6 ± 33.62	72.4 ± 89.51	39.6 ± 15.35
Symptomatic GERD	27.4 ± 5.95	27.8 ± 6.08	NA
EO healing	NA	38.1 ± 15.06	39.6 ± 15.35
EO maintenance	52.9 ± 54.92	138.1 ± 62.57	NA
Long-term safety	NA	276.2 ± 134.67	NA

EO, erosive oesophagitis; GERD, gastro-oesophageal reflux disease; MR, modified release.
* Lansoprazole was used only in the two EO healing studies with duration of 8 weeks.

persistent significant disability or birth-defect or were life-threatening or considered medically significant by the investigators.

Adverse events resulting in premature discontinuation of study drug were tracked. AEs of special interest were defined as those that were considered possibly

associated with PPI use, of public safety concern or based on sporadic results seen in one or more dexlansoprazole MR studies. They included potential cardiovascular events, upper respiratory tract infections (URTIs), lower respiratory tract infections, hepatic enzyme abnormalities, cholelithiasis/cholecystitis, gastric polyps, hip and vertebral fracture and calcium homeostasis, anaemia and *Clostridium difficile* diarrhoea.

Clinical laboratory tests, vital signs and electrocardiograms

Routine laboratory evaluations, including haematology (complete blood counts), chemistry (metabolic profile) and urinalysis, were performed at protocol-specified visits and were sent to a central laboratory. Patients were to fast for a minimum of 10 h before the collection of laboratory samples, including serum gastrin levels. However, all laboratory results, including serum gastrin, were included in the analysis regardless of whether patients had fasted.

Changes in laboratory values that might be clinically important were defined *a priori*. These values were termed potentially clinically important (PCI) and were reviewed and summarized to determine whether they represented a pattern of adverse drug reaction.

Vital signs were evaluated at each study visit. Baseline and end-of-treatment electrocardiograms (ECGs) were performed on a subset of patients (n = 535) in one of the symptomatic GERD studies.

Gastric biopsies

Four gastric biopsies were obtained during endoscopy at baseline for 1 of the phase 3 symptomatic nonerosive GERD studies during both EO healing studies and at the final visit of the phase 3 maintenance of healed EO studies and the long-term safety study. Two mucosal biopsies were taken from the gastric antrum. These biopsies were taken distally on the lesser curvature, 1 to 2 cm proximal to the pyloric sphincter. The other 2 mucosal biopsies were taken from the fundus/body (greater and lesser curvature) of the stomach. Biopsies were placed in 10% buffered formalin and shipped to the Cleveland Clinic Foundation (Cleveland, OH, USA) for centralized processing and analysis. All biopsies were evaluated for the presence of active and chronic inflammation, atrophy, intestinal metaplasia, changes in endocrine cell density and enterochromaffin-like (ECL) cell hyperplasia.

Statistical methods

Data from all patients who received ≥1 dose of study drug were included in the safety analyses; P values ≤0.05 were reported as statistically significant. A conditional exact test based on the Poisson distribution was used for pairwise comparisons of the incidence rates between treatment groups for each MedDRA HLT and for total patients with ≥1 AE. Relative risks and the corresponding 95% CIs were calculated to compare common adverse effects between treatment groups.

Clinical laboratory evaluations and vital signs were not integrated for all phase 3 studies because of the differences among the studies in visits and durations. Thus, these evaluations were analysed by indication. For mean changes from baseline, pairwise comparisons between treatment groups were made using contrast statements within the framework of an analysis of variance model. For patients with PCI values and shifts in laboratory values relative to normal range, pairwise comparisons between treatment groups were made using the Fisher exact test. For AE incidences and mean changes in laboratory values, subgroup comparisons were also made for age, gender, body mass index (BMI), race and certain comorbid conditions.

RESULTS

Adverse events

Phase 3 clinical trials for dexlansoprazole MR began in December 2005 and were completed by May 2007, with the exception of the long-term safety study. This study was initiated in January 2006 and interim data up to October 2007 were used for this analysis. In all phase 3 studies combined, the number of patients with ≥1 treatment-emergent AE per 100 PM of exposure was the highest among placebo patients (24.49), followed by lansoprazole patients (21.06) and dexlansoprazole MR patients (15.64–18.75) across dose groups. The most frequent treatment-emergent AEs reported among all patients taking dexlansoprazole MR (≥1 patient per 100 PM of exposure by MedDRA HLT) were diarrhoea, URTIs, gastrointestinal and abdominal pains, nausea and vomiting, headaches, and flatulence, bloating and distention (Figure 1).

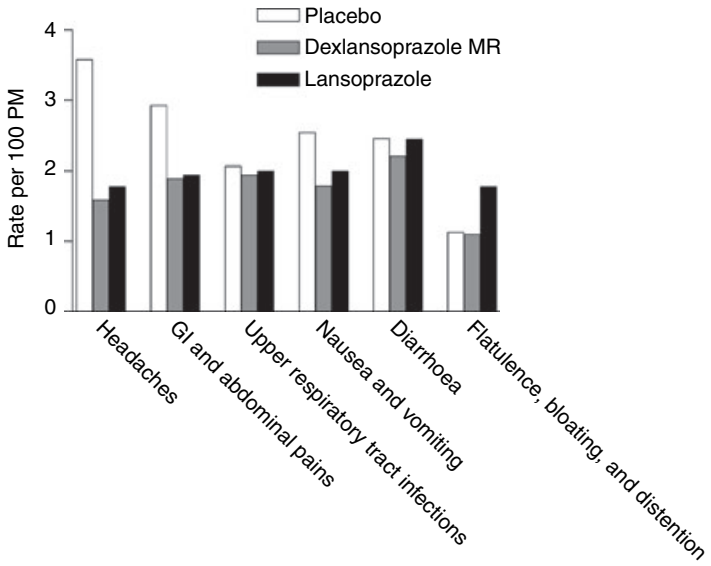

Figure 1. Treatment-emergent adverse events experienced by ≥1 patient per 100 PM of exposure in patients receiving dexlansoprazole MR in all phase 3 studies. GI, gastrointestinal; MR, modified release; PM, patient-months.

For most of the common treatment-emergent AEs by MedDRA preferred term, there were no statistically significant differences between patients receiving dexlansoprazole MR compared with those receiving placebo (Figure 2) or lansoprazole (Figure 3). The relative risks for nausea, headache, dyspepsia, abdominal tenderness and EO were significantly lower in the dexlansoprazole MR group compared with the placebo group (Figure 2); abdominal distension, hiatal hernia, nasopharyngitis and Barrett's oesophagus were significantly lower for the dexlansoprazole MR group compared with the lansoprazole group (Figure 3). No statistically significantly higher incidence of the most frequent MedDRA HLTs was seen in any dexlansoprazole MR dose groups compared with either the placebo group or the lansoprazole group.

The treatment-emergent AE profiles for each indication and in the long-term safety study were similar to that of all the phase 3 studies combined. However, a significantly greater percentage of patients in the dexlansoprazole MR 90-mg dose group (7.9%) in the symptomatic GERD studies experienced URTIs compared with the placebo (2.6%), dexlansoprazole MR 30-mg (3.5%), or dexlansoprazole MR 60-mg (3.7%) treatment groups. Most URTIs were mild-to-moderate and associated with a history of seasonal allergies; they were, therefore, deemed unrelated to study drug. There were no statistically significant differences between groups in the rates of lower respiratory tract infections. A dose-dependent increase in diarrhoea was observed in the studies of maintenance of healed EO; most cases were mild-to-moderate and did not

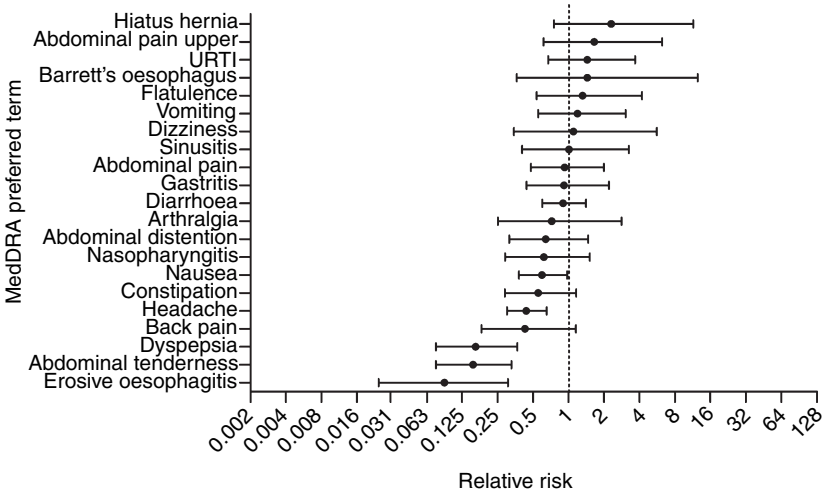

Figure 2. Relative risk (±95% CI in logarithmic scale) of the most common treatment-emergent adverse events by patient-months of exposure in patients receiving dexlansoprazole MR 30, 60 or 90 mg compared with placebo in phase 3 studies by MedDRA preferred term. MedDRA, Medical Dictionary for Regulatory Activities; MR, modified release; URTI, upper respiratory tract infection.

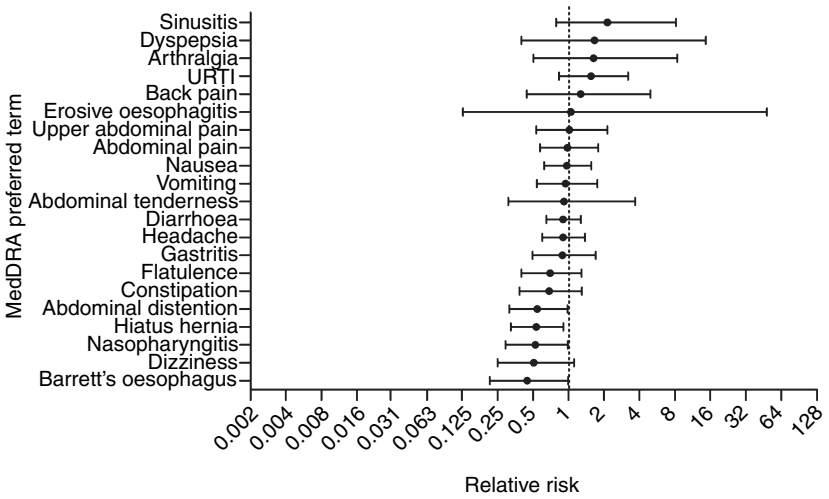

Figure 3. Relative risk (±95% CI in logarithmic scale) of the most common treatment-emergent adverse events by patient-months of exposure in patients receiving dexlansoprazole MR 30, 60, or 90 mg compared with lansoprazole 30 mg in phase 3 studies by MedDRA preferred term. MedDRA, Medical Dictionary for Regulatory Activities; MR, modified release; URTI, upper respiratory tract infection.

result in premature discontinuation. Dose-dependent increases in diarrhoea observed in the EO maintenance study groups were not replicated by the results from other indications. The incidence of overall AEs and most frequent AEs (e.g. diarrhoea, URTIs and headaches) was higher for patients using nonsteroidal anti-inflammatory drugs (NSAIDs) compared with nonusers across indications.

The only notable finding in the subgroup analyses evaluating AEs by age, gender, BMI, race and comorbid conditions was an increase in diarrhoea observed with increasing age in the dexlansoprazole MR 90-mg and lansoprazole 30-mg treatment groups in the EO healing studies.

In all phase 3 studies combined, 61 patients (placebo, $n = 2$; dexlansoprazole MR, $n = 52$; and lansoprazole, $n = 7$) experienced a nonfatal SAE. When adjusted for exposure, the number of patients with ≥1 treatment-emergent, nonfatal SAE per 100 PM ranged from 0.43 to 0.54 across dexlansoprazole MR dose groups and was 0.39 in the lansoprazole 30-mg treatment group and 0.19 in the placebo group. No statistically significant differences were found between any dexlansoprazole MR dose group and either the placebo or lansoprazole group. No dose-related trends were observed and a majority of nonfatal SAEs were considered unrelated to study drug. Nonfatal SAEs (MedDRA PTs) occurring in ≥2 patients in the dexlansoprazole MR group included: cholecystitis, cholelithiasis, coronary artery disease, endometriosis, fall, gastroenteritis, migraine, myocardial infarction, noncardiac chest pain, pneumonia, sepsis and syncope. No SAE was reported in more than five patients of the 4270 treated with dexlansoprazole MR.

Seven patients died in phase 3 studies [dexlansoprazole MR 60 mg, $n = 5$ (0.09/100 PM); dexlansoprazole MR 90 mg, $n = 1$ (0.02/100 PM); lansoprazole 30 mg, $n = 1$ (0.06/100 PM)]. The causes of death were malignant disease ($n = 2$), postsurgery complications ($n = 2$), methadone overdose ($n = 1$), respiratory failure ($n = 1$), and hepatic failure ($n = 1$) in a patient with a history of alcohol abuse and other underlying conditions. All deaths were considered by the investigators to be unrelated to study drug. No trends were identified regarding the types or onset of treatment-emergent AEs leading to death or the cause of death.

No significant differences in the number of patients per 100 PM with ≥1 treatment-emergent AE of special interest were found between any dexlansoprazole MR dose group and either the placebo or lansoprazole treatment group. A total of 20 gastric polyps were recorded as AEs (placebo, $n = 1$; lansoprazole 30 mg, $n = 1$; and dexlansoprazole MR 30 mg, $n = 1$; 60 mg, $n = 13$; and 90 mg, $n = 4$). Although the incidence of gastric polyps was increased after treatment in the dexlansoprazole MR group, this increase was not dose-related after adjusting for the number of endoscopies performed.

Premature discontinuations

A significantly greater number of patients per 100 PM in the placebo-treated group (3.86) prematurely discontinued treatment because of AEs compared with the dexlansoprazole MR 30-mg (0.96), 60-mg (1.48) and 90-mg (1.46) groups (Table 4). This was primarily because of the greater number of patients who experienced gastrointestinal-related AEs in the placebo

Table 4. Treatment-emergent adverse events leading to premature discontinuation in phase 3 studies

Group	Patients with events, *n* (rate per 100 PM)	Patients, *n*	Average PM
Dexlansoprazole MR	147 (1.43)	4270	2.4
30 mg	9 (0.96)*	455	2.1
60 mg	78 (1.48)*	2311	2.3
90 mg	60 (1.46)*	1864	2.2
Lansoprazole 30 mg	18 (1.00)	1363	1.3
Placebo	41 (3.86)	896	1.2

MR, modified release; PM, patient-months of exposure.
* Statistically significantly different vs. placebo ($P \leq 0.05$).

group. There was no single treatment-emergent AE that led to premature discontinuation of study drug in ≥0.5 patients per 100 PM in any dexlansoprazole MR dose group or in the lansoprazole treatment group. The most common treatment-emergent AE leading to premature discontinuation of study drug in dexlansoprazole MR dose groups was diarrhoea (0.37/100 PM).

Clinical laboratory values, vital signs and electrocardiograms

Overall, mean changes from baseline in haematology, chemistry and urinalysis values were small. A few statistically significant differences were observed between treatment groups at isolated time points for some parameters, but no pattern of clinical concern emerged. In the maintenance studies, decreases from baseline in haemoglobin, haematocrit and platelet count were observed in the dexlansoprazole MR treatment groups; however, these mean decreases were small and remained within normal limits. For all other haematological parameters, no consistent trend was noted among treatment groups for individual patients with significant changes and no dose-response was observed for shifts in values (relative to normal ranges). Higher incidences of low haemoglobin that were considered PCI (≤11.5 g/dL for men, ≤9.5 g/dL for women, or ≥2 g/dL decrease for either gender) were observed in the maintenance of EO healing studies (2% placebo, 6–9% across dexlansoprazole MR dose groups) and in the long-term safety study (6% of patients in each dexlansoprazole MR dose group). Although no common aetiologies were noted in patients with PCI haemoglobin values, mean decreases were small. Few patients with low haemoglobin in the maintenance of healed EO studies (12/896) and the long-term safety study (3/313) had final haemoglobin values that were less than the lower limit of normal or ≥1 g/dL lower than the baseline haemoglobin value. Red blood count morphology for seven of these patients was normocytic, four showed anisocytosis and 1 showed macrocytosis. Small mean decreases in haemoglobin (0.08–0.14 g/dL below baseline) across dexlansoprazole MR dose groups were also observed in the symptomatic GERD studies, but not in the EO healing studies.

For chemistry variables, mean changes from baseline in chemistry parameters were small. No consistent trend was noted among treatment groups for individual patients with significant changes and no dose-response was observed for shifts in values. The percentage of patients with elevated liver enzyme values (≥3 × upper limit of normal (ULN) or ≥5 × ULN for alanine aminotransferase (ALT) or aspartate aminotransferase (AST); ≥3 × ULN for ALT and AST concurrently) ranged from 0% to <1% across treatment groups in the phase 3 symptomatic nonerosive GERD, healing of EO and long-term safety studies and from 0% to 2% in the Phase 3 maintenance of healed EO studies. No patient had hepatic enzyme elevations ≥10 × ULN. No patient in any phase 3 study had concomitant elevations of ALT or AST and total bilirubin or concomitant elevations of ALT or AST and alkaline phosphatase. No clinically meaningful results were observed in the analysis of mean change from baseline in urinalysis parameters.

The percentage of patients with PCI vital sign values was ≤2% in all phase 3 treatment groups. No statistically significant differences in the percentage of patients with PCI vital sign values were found between any dexlansoprazole MR dose group and either the placebo or lansoprazole dose group. No clinical concerns were noted regarding QT intervals and no relevant AEs were associated with ECG changes. Mean changes in the QTcF and QTcB intervals for all dexlansoprazole MR dose groups were <2 milliseconds.

Furthermore, there were no significant differences in any subgroup analyses assessing mean changes in laboratory parameters by age, gender, BMI, race and comorbid conditions.

Serum gastrin

As expected, mean serum gastrin levels increased in all PPI dose groups (lansoprazole 30 mg and

dexlansoprazole MR 30, 60, and 90 mg) and were significantly higher than in the placebo group. Gastrin levels increased 1- to 2-fold during the first 3 months of receiving dexlansoprazole MR in the maintenance studies and then generally stabilized for the remainder of treatment (Figure 4a). Importantly, increases in gastrin levels were not dependent on the dose of dexlansoprazole MR received. Patients who were randomized to placebo in the EO maintenance study after successful healing on active treatment (either dexlansoprazole MR or lansoprazole) had mean gastrin levels return to baseline within the first month of the study, regardless of which treatment they had received for EO healing (Figure 4b).

The pattern of increase and stabilization of gastrin levels observed in the long-term safety study was similar to that observed in the EO maintenance studies (Figure 5). Patients in the long-term safety study had received dexlansoprazole MR or placebo during earlier trials to treat symptomatic nonerosive GERD. Differences in mean changes in serum gastrin levels between the dexlansoprazole MR dosage groups were not statistically significant; thus, the data do not support a dose-dependent effect of dexlansoprazole MR on serum gastrin levels.

Gastric biopsy

In the maintenance of healed EO studies, no clinically concerning differences in gastric biopsy results were observed between any of the dexlansoprazole MR dose groups and placebo. In the long-term safety study, chronic gastritis (in either antral or fundic tissue) was the most commonly reported abnormality in 31% and 36% of the patients in the dexlansoprazole MR 60- and 90-mg groups respectively. There were no reports of ECL hyperplasia in the phase 3 studies of 6 months to 1 year in duration. Among the studies for maintenance of EO healing and long-term safety, 5 (0.8%) of the 653 dexlansoprazole MR patients with baseline and final visit biopsy results, and with normal antral biopsies at baseline, had a diagnosis of intestinal metaplasia without dysplasia or neoplasia at the final visit. These changes did not appear to be dose-dependent; no trends were observed.

DISCUSSION

With a safety profile similar to the racemate lansoprazole,[26] dexlansoprazole MR was accepted by most

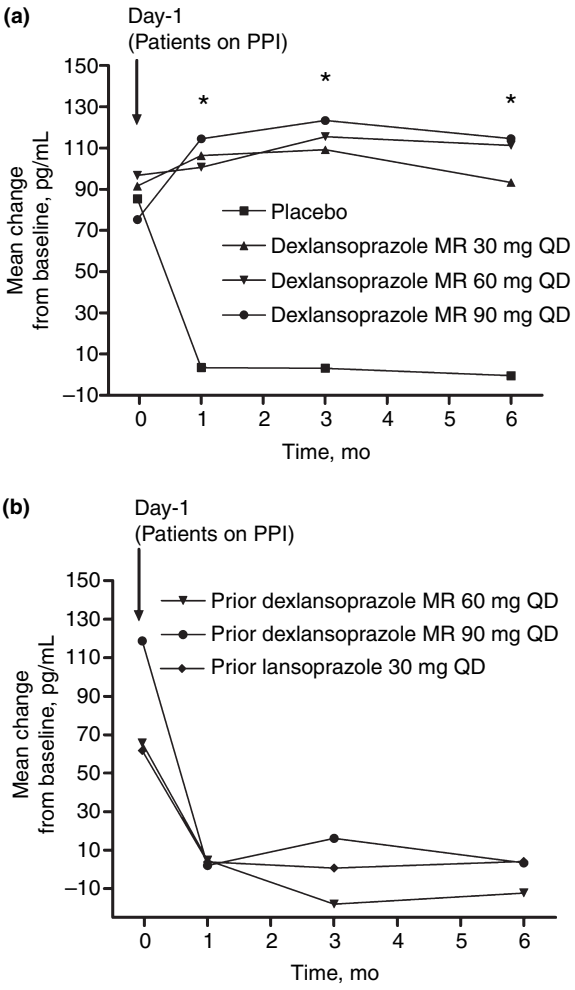

Figure 4. Mean changes from baseline in serum gastrin in the phase 3 maintenance of healed erosive oesophagitis (EO) studies. Baseline was the last measurement before the first dose of study drug in the preceding EO healing studies, before patients received any study drug. The first values for each treatment group are for day −1, the last measurement before the first dose in the maintenance studies and represent an assessment of EO healing. The upper limit of normal for serum gastrin is 111 pg/mL. (a) All patients in the maintenance trials. The number of patients analysed (at day −1, month 1, month 3, and month 6): placebo, n = 35–207; dexlansoprazole MR 30 mg, n = 16–111; dexlansoprazole MR 60 mg, n = 35–267; and dexlansoprazole MR 90 mg, n = 16–110. (b) Patients randomized to placebo stratified by the treatment they received in the preceding EO healing study. The number of patients analysed (at day −1, month 1, month 3 and month 6): dexlansoprazole MR 60 mg, n = 9–64; dexlansoprazole MR 90 mg, n = 14–82; and lansoprazole 30 mg, n = 12–61. *$P \leq 0.05$ dexlansoprazole MR 30, 60, and 90 mg vs. placebo. MR, modified release; PPI, proton pump inhibitor; QD, once daily.

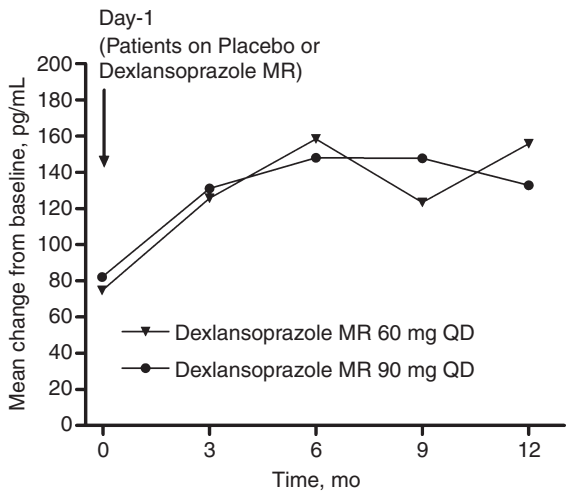

Figure 5. Mean changes from baseline in serum gastrin in the phase 3 long-term safety study. Baseline was taken before dexlansoprazole MR or placebo treatment of symptomatic gastro-oesophageal reflux disease in the preceding 1-month study. Day −1 is the last available observation from that study; values include those for patients on dexlansoprazole MR as well as placebo. No statistically significant differences between treatment groups were observed. The number of patients analysed at day −1, month 3, month 6, month 9 and month 12 were 115, 113, 107, 96 and 81 respectively, for dexlansoprazole MR 60 mg, and 120, 107, 96, 86 and 67 for dexlansoprazole MR 90 mg. MR, modified release; QD, once daily.

patients throughout the global clinical trial programme. The overall incidence of AEs was similar across treatment groups. A dose-dependent increase in diarrhoea was observed in patients receiving dexlansoprazole MR in the maintenance of healed EO studies. This finding is similar to a dose-dependent increase observed with lansoprazole.[27] No other dose-dependent increases in AEs were noted. As expected, placebo-treated patients experienced a higher number of other gastrointestinal-related AEs. Whereas previous studies with PPIs have shown an association with lower respiratory tract infections,[28] such observations were not seen in this analysis. It appears that the increased incidence of URTIs seen with dexlansoprazole MR 90 mg does not result in clinically relevant disease as few patients received treatment with antibiotics. Decreases in mean haemoglobin, hematocrit and platelet count were observed in the maintenance of healed EO studies. However, these changes were not accompanied by changes in other haematological parameters and were not consistent across studies. The incidence of SAEs was low and displayed no clear pattern. No significant findings were observed for AEs of special interest. A non–dose-related increase in gastric polyps in patients receiving dexlansoprazole MR was noted, but benign fundic polyps are known to be associated with long-term PPI therapy.[29–32] Seven patients died during treatment; however, none of the deaths was deemed to be related to the study drug by the investigator.

The increases in gastrin levels observed were not unexpected. Increases in serum gastrin are an expected physiological response to the increase in intragastric pH resulting from PPI treatment;[33] gastrin is therefore a marker of acid suppression.[34] In the dexlansoprazole MR studies, increased gastrin levels were reversed shortly after patients switched to placebo. In the published literature, no safety issues have been associated with long-term gastrin elevation in humans[35] nor was any dysplasia or metaplasia observed in gastric biopsies of patients receiving dexlansoprazole MR in the long-term safety study. Furthermore, the lack of concerning findings regarding gastric biopsies is consistent with what was found with the racemate lansoprazole in long-term studies.[26]

The higher doses required for the DDR formulation to prolong exposure of patients to dexlansoprazole did not pose a clinical concern. Multiple daily dosing of conventional PPIs has been reported in up to 42% of patients with heartburn or acid regurgitation[36] and high PPI doses have been given for other acid-related medical conditions (e.g. Zollinger–Ellison syndrome, gastrinomas, reflux oesophagitis) without significant safety concerns.[2, 3, 7, 37, 38] In phase 1 studies, higher doses of dexlansoprazole MR (up to 120 mg in multiple doses and 300 mg in single doses) were administered to healthy volunteers. There were no adverse effects on QT interval using single doses ≤300 mg in healthy volunteers.[13] No safety issues arose in four separate drug-drug interaction studies using dexlansoprazole MR 90 mg (in which no pharmacokinetic interactions were seen with diazepam, phenytoin, theophylline, or warfarin and no pharmacodynamic interactions were seen with warfarin).[18] In addition, no clinically relevant concerns were noted in patients with mild-to-moderate hepatic impairment receiving a single dose of dexlansoprazole MR 60 mg,[17] although the package insert suggests 30 mg QD in patients with moderate hepatic impairment.

In conclusion, the combined phase 3 clinical trial data from approximately 4300 patients treated with

dexlansoprazole MR (30, 60, and 90 mg) showed that the drug had a safety profile comparable to lansoprazole 30 mg.

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