

# Dexlansoprazole Modified Release In Erosive Oesophagitis and Non-Erosive Reflux Disease

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## Abstract

Dexlansoprazole modified release (dexlansoprazole MR) is an orally administered delayed-release formulation of the *R*-enantiomer of the proton pump inhibitor lansoprazole that is effective in improving the healing of all grades of erosive oesophagitis, maintaining the healing of erosive oesophagitis and in the treatment of symptomatic non-erosive reflux disease (NERD).

In two large, identical, 8-week, randomized, double-blind, multicentre phase III trials, dexlansoprazole MR 60 mg once daily achieved complete healing in  $\geq 92\%$  of patients with all grades of erosive oesophagitis (primary endpoint) and was non-inferior to lansoprazole 30 mg once daily using life-table analysis.

Moreover, in a randomized, double-blind, multicentre phase III trial in patients with healed erosive oesophagitis, dexlansoprazole MR 30 mg once daily was significantly more effective than placebo in maintaining healing following 6 months' treatment (primary endpoint).

In addition, the proportion of 24-hour heartburn-free days (primary endpoint) was significantly greater in recipients of dexlansoprazole MR 30 mg once daily than in recipients of placebo following 4 weeks' treatment in a large, randomized, double-blind, multicentre phase III trial in patients with NERD.

Dexlansoprazole MR 30 or 60 mg once daily was generally well tolerated in a pooled analysis of clinical trials of up to 12 months' duration.

Features and properties of dexlansoprazole modified release (MR) [Dexilant™]		
Indication		
Healing of all grades of erosive oesophagitis, maintenance of healed erosive oesophagitis and the management of symptomatic non-erosive reflux disease (NERD) in adults		
Mechanism of action		
Proton pump inhibitor	Inhibits gastric acid secretion	
Dosage and administration		
Healing of erosive oesophagitis	60 mg for up to 8 wk	
Maintenance of healed erosive oesophagitis	30 mg for up to 6 mo	
Symptomatic NERD	30 mg for 4 wk	
Route of administration	Oral	
Frequency of administration	Once daily	
Pharmacokinetic profile of dexlansoprazole MR 30 or 60 mg once daily for 5 d in 45 healthy subjects. All values are means unless stated otherwise		
	30 mg	60 mg
Peak plasma concentration (C <sub>max</sub> ) [ng/mL]	658	1388
Time to C <sub>max</sub> (h)	4.45	4.88
Area under the plasma concentration-time curve from time zero to 24 h (ng • h/mL)	3275	6400
Harmonic terminal elimination half-life (h)	1.49	1.69
Apparent oral clearance (L/h)	11.4	11.6
Most frequent (incidence ≥2%) treatment-emergent adverse events that occurred with a higher frequency than with placebo		
Diarrhoea, abdominal pain, nausea, upper respiratory tract infection, vomiting, flatulence		

Gastro-oesophageal reflux disease (GORD) is defined as the abnormal passage of gastric contents into the oesophagus.<sup>[1]</sup> GORD can be broadly classified into three categories: erosive oesophagitis, non-erosive reflux disease (NERD) and Barrett's oesophagus.<sup>[2]</sup> However, there is some evidence that these categories are a continuum and that, if untreated, patients may progress from non-erosive to erosive oesophagitis.<sup>[3]</sup> Erosive oesophagitis is the most frequent complication of GORD and heartburn is the most frequent symptom of NERD.<sup>[4-6]</sup>

Although the underlying causes of GORD are multifactorial, the primary goal of antisecretory therapy is to maintain an elevated intragastric pH for the longest possible time.<sup>[5,7,8]</sup> Specifically, treatments that maintain an intra-oesophageal pH >4 for the greatest proportion of a 24-hour acid-exposure period are associated with optimal oesophageal healing and symptomatic relief of reflux disease.<sup>[9]</sup>

Proton pump inhibitors (PPIs) are effective and generally well tolerated inhibitors of acid secretion from parietal cells.<sup>[10]</sup> As a consequence, PPIs are now recognised as the preferred treatment option for patients with reflux disease, as they provide the most effective symptomatic relief and the highest rates of healing or erosive oesophagitis.<sup>[8,10]</sup> However, as a result of rapid delivery to the small intestine, equally rapid elimination through renal excretion and hepatic metabolism and irreversible binding to the proton pump, PPIs are unable to completely control gastric pH over a 24-hour period, even with multiple oral doses.<sup>[11]</sup>

Dexlansoprazole is the *R*-enantiomer of the well established PPI lansoprazole. Although the two enantiomers are equipotent in terms of activity, as a result of its decreased clearance rate, the *R*-enantiomer constitutes >80% of circulating lansoprazole, following oral administration.<sup>[12,13]</sup> Consequently, dexlansoprazole displays a higher systemic exposure than lansoprazole.<sup>[12]</sup>

Dexlansoprazole modified release (dexlansoprazole MR) [Dexilant<sup>TM</sup>] is a novel formulation of dexlansoprazole in enteric-coated granules within a gelatin capsule, which is designed to deliver the drug in two discrete phases, thus ex-

tending the period of systemic exposure following oral administration.<sup>[14,15]</sup> In the initial phase, dexlansoprazole is released into the proximal duodenum, with release of the drug during the second phase being into the distal portion of the small intestine.<sup>[14,15]</sup>

Dexlansoprazole MR is approved in the US for the healing of all grades of erosive oesophagitis, maintaining healing of erosive oesophagitis and the treatment of symptomatic NERD in adult patients.<sup>[16]</sup> This article provides an overview of the pharmacological profile of dexlansoprazole MR, and reviews its clinical efficacy and tolerability in patients with erosive oesophagitis or NERD.

Medical literature on the use of dexlansoprazole MR in erosive oesophagitis and NERD was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database). Additional references were identified from reference lists of published articles. Searches were last updated 28 June 2010.

## 1. Pharmacodynamic Profile

The pharmacodynamic properties of dexlansoprazole MR were evaluated in two separate randomized, open-label, multiple-dose studies in healthy volunteers that used a pooled analysis of data from both approved and unapproved dosages.<sup>[17]</sup> This section focuses on data for the approved dosages of dexlansoprazole MR (30 and 60 mg once daily; see section 5) from these studies, which were reported separately as a review<sup>[15]</sup> and in the manufacturer's prescribing information,<sup>[16]</sup> supplemented by data from other studies in patients with erosive oesophagitis or NERD<sup>[18]</sup> or healthy volunteers.<sup>[19]</sup>

- Dexlansoprazole blocks the final step in gastric acid secretion in parietal cells by selective inhibition of the H<sup>+</sup>/K<sup>+</sup>-ATPase enzyme (the proton pump).<sup>[14]</sup> Both basal and stimulated gastric acid production are suppressed by dexlansoprazole.<sup>[14]</sup>
- Following 5 days' treatment, oral dexlansoprazole MR effectively suppressed gastric acid production.<sup>[17]</sup> A once-daily regimen of dexlansoprazole MR 60 mg resulted in a significantly

greater mean 24-hour intragastric pH than lansoprazole 30 mg once daily (pH 4.55 vs 4.13;  $p < 0.001$ ) in 40 healthy volunteers.<sup>[15,16]</sup>

- Moreover, a significantly greater increase in the proportion of time with a 24-hour intragastric pH >4 was observed in recipients of once-daily dexlansoprazole MR 60 mg than in lansoprazole 30 mg recipients (71% vs 60%;  $p < 0.01$ ) after 5 days of treatment.<sup>[15,16]</sup>
- A pooled analysis of patients treated for the maintenance of healed erosive oesophagitis receiving dexlansoprazole MR once daily for 6 months showed that mean fasting serum gastrin levels were increased from baseline by 1- to 2-fold and the mean changes were significantly ( $p \leq 0.05$ ) higher than in patients receiving placebo.<sup>[18]</sup> A longer-term analysis for up to 12 months showed similar results, with the biggest increase in gastrin levels occurring during the first 3 months of treatment and levels stable thereafter; within 1 month of discontinuation, gastrin levels returned to baseline.<sup>[16,18]</sup>
- No clinically significant effects on enterochromaffin-like cells were observed following treatment with dexlansoprazole MR 30 or 60 mg once daily for up to 12 months in adult patients.<sup>[16]</sup>
- Furthermore, no clinically significant prolongation of the mean maximum QT/corrected QT interval was observed in healthy adults receiving a single dose of dexlansoprazole at the higher than approved doses of 90 or 300 mg.<sup>[19]</sup>

## 2. Pharmacokinetic Profile

This section focuses on pharmacokinetic data relating to the approved dosages of dexlansoprazole MR from one of the two pharmacodynamic studies in healthy volunteers described in section 1,<sup>[17]</sup> with additional information provided from the manufacturer's prescribing information.<sup>[16]</sup> Dexlansoprazole MR 30 or 60 mg was administered once daily, following a minimum 10-hour fast, for a period of 5 days.<sup>[17]</sup>

- The pharmacokinetics of dexlansoprazole MR are dose proportional and time independent.<sup>[15]</sup> Oral dexlansoprazole 30 and 60 mg is rapidly absorbed (the initial peak occurs approximately 1–2 hours after administration), with a mean

maximum plasma concentration of 658 and 1388 ng/mL reached at a mean time of 4.45 and 4.88 hours, and a mean area under the plasma concentration-time curve from time zero to 24 hours of 3275 and 6400 ng • h/mL.<sup>[17]</sup>

- Dexlansoprazole is highly plasma protein bound (96.1–98.8%) in healthy volunteers, with an apparent volume of distribution of 40.3 L in patients with GORD.<sup>[16]</sup>

- No clinically significant effects on the pharmacokinetics of dexlansoprazole were observed following administration of dexlansoprazole MR under fasted or fed conditions, or with regard to the timing of food.<sup>[20,21]</sup> Consequently, oral dexlansoprazole MR may be administered with or without food.<sup>[16]</sup>

- Dexlansoprazole is metabolized extensively in the liver by oxidation and reduction to inactive sulfate, glucuronide and glutathione metabolites.<sup>[16]</sup> Metabolism occurs predominantly via the cytochrome P450 (CYP) isoenzymes CYP2C19 and CYP3A4.<sup>[16]</sup> Dexlansoprazole is the predominant circulating component in plasma, regardless of CYP2C19 metabolizer status.<sup>[16]</sup>

- Following oral administration in healthy volunteers, 51% of the [<sup>14</sup>C]dexlansoprazole dose was eliminated in urine and 48% in faeces.<sup>[16]</sup> The apparent clearance of dexlansoprazole MR 30 or 60 mg once daily was 11.4 and 11.6 L/h after 5 days of treatment,<sup>[16]</sup> and the harmonic mean terminal half-life was 1.49 and 1.69 hours.<sup>[17]</sup>

- No clinically significant effect in healthy volunteers on the pharmacokinetics of diazepam, phenytoin and theophylline was observed following coadministration with dexlansoprazole MR 90 mg once daily and the pharmacokinetic profile of other drugs metabolized via CYP2C19, CYP2C9, CYP1A2 and perhaps CYP3A4 is unlikely to be affected.<sup>[22]</sup>

- Other PPIs, such as omeprazole, may affect the pharmacokinetic profile of clopidogrel and reduce antiplatelet activity.<sup>[23]</sup> There are no drug interaction data for dexlansoprazole and clopidogrel; however, as dexlansoprazole does not inhibit the activity of CYP2C19, it is not expected to affect the pharmacokinetics of clopidogrel.

- Coadministration of dexlansoprazole MR 90 mg and warfarin 25 mg did not affect the

pharmacokinetics of warfarin or the international normalized ratio (INR).<sup>[16,22]</sup> Nonetheless, concomitant use of PPIs with warfarin may increase INRs and prothrombin times, and patients may require monitoring.<sup>[16]</sup>

- Caution is also advised when coadministering dexlansoprazole MR with tacrolimus or drugs with pH-dependent absorption pharmacokinetics (e.g. ampicillin esters, digoxin, iron salts and ketoconazole).<sup>[16]</sup> Dexlansoprazole MR should not be coadministered with atazanavir, the absorption of which is dependent upon gastric acid, as the systemic exposure of atazanavir may be reduced.<sup>[16]</sup>

- Differences in the pharmacokinetic profile of dexlansoprazole according to age and sex are not clinically significant, and dosage adjustments are not necessary.<sup>[16]</sup> The pharmacokinetics of dexlansoprazole have not been evaluated in patients under 18 years of age.<sup>[16]</sup>

- Exposure to dexlansoprazole is approximately 2-fold higher in patients with moderate hepatic impairment (Child-Pugh class B) than in those with normal hepatic function and a maximum dosage of dexlansoprazole MR 30 mg once daily should be considered.<sup>[16]</sup> No dosage adjustments are necessary in patients with mild hepatic impairment (Child-Pugh class A); studies in patients with severe hepatic impairment (Child-Pugh class C) have not been conducted.<sup>[16]</sup> No dosage adjustments are necessary in patients with renal impairment.<sup>[16]</sup>

### 3. Therapeutic Efficacy

The therapeutic efficacy of oral dexlansoprazole MR has been evaluated in the healing<sup>[24]</sup> and maintenance of healing<sup>[25]</sup> of erosive oesophagitis and in the treatment of symptomatic NERD in randomized, double-blind, multicentre phase III trials in adult patients aged  $\geq 18$  years.<sup>[13]</sup>

#### Erosive Oesophagitis

The healing of erosive oesophagitis was evaluated in two large, identical, phase III trials in adult patients ( $n > 2000$  in each trial), which were individually reported in the same publica-

tion.<sup>[24]</sup> Patients with endoscopically proven erosive oesophagitis of all grades ( $\approx 30\%$  were Los Angeles [LA] grade C and D) were eligible to receive 8 weeks' treatment with dexlansoprazole MR 60 (n=680 and 694) or 90 mg (n=668 and 687), or lansoprazole 30 mg (n=690 and 673) once daily.<sup>[24]</sup> A subset of patients with healed erosive oesophagitis at study end were further evaluated for the maintenance of healing in a 6-month, randomized, double-blind, placebo-controlled, multicentre, phase III trial (n=445).<sup>[25]</sup> In the maintenance study, patients received dexlansoprazole MR 30 mg (n=140) or 60 mg (n=158) or placebo (n=147) once daily.<sup>[25]</sup> The dosages of dexlansoprazole MR 90 mg once daily for the healing of erosive oesophagitis and dexlansoprazole MR 60 mg once daily for the maintenance of healing are not approved (section 5) and, thus, these data are not discussed further.<sup>[16]</sup>

Exclusion criteria included *Helicobacter pylori*-positive status, pregnancy, breast-feeding, coexisting diseases of the oesophagus, active gastric or duodenal ulcers, the use of other PPIs or histamine H<sub>2</sub>-receptor antagonists or NSAIDs, or acute upper gastrointestinal haemorrhage within 4 weeks of screening.<sup>[24,25]</sup> Additionally, patients with uncontrolled systemic disease, not practising double-barrier contraception, or receiving sucralfate, misoprostol, prokinetic agents or anticoagulant therapy were excluded from the maintenance of healing trial.<sup>[25]</sup>

The primary endpoints were the proportion of patients with complete healing of erosive oesophagitis at 8 weeks<sup>[24]</sup> and the proportion with maintained healing at 6 months,<sup>[25]</sup> as assessed by endoscopy. Week 4 healing rates and the proportion of patients with LA grade C or D erosive oesophagitis at baseline achieving complete healing at 8 weeks were defined as secondary endpoints in the healing studies.<sup>[24]</sup> All randomized patients with endoscopically proven erosive oesophagitis who received at least one dose of study medication were included in the modified intent-to-treat (ITT) analyses.<sup>[24,25]</sup> Efficacy analyses and the estimated cumulative rate of maintained healing were assessed using life-table as the primary analysis method and crude rates as an additional analysis method.<sup>[24,25]</sup> Crude rate is

the simple proportion of patients with healed erosive oesophagitis, whereas life-table analysis accounts for the time taken to heal and censored data.<sup>[24,25]</sup> Noninferiority for dexlansoprazole MR versus lansoprazole in healing rates at week 8 was achieved if the lower bound 95% confidence interval was more than  $-10$ .<sup>[24]</sup>

- Dexlansoprazole MR 60 mg once daily provided effective healing of erosive oesophagitis after 8 weeks' treatment in two identically designed studies.<sup>[24]</sup> Using life-table analysis,  $\geq 92\%$  of dexlansoprazole MR 60 mg once daily recipients achieved complete healing of erosive oesophagitis at week 8 (primary endpoint) versus  $\geq 86\%$  of lansoprazole 30 mg once daily recipients, with no significant between-group difference in each individual study (figure 1).<sup>[24]</sup>

- In addition, dexlansoprazole MR 60 mg was shown to be noninferior to lansoprazole 30 mg in terms of erosive oesophagitis healing rates in both studies (figure 1).<sup>[24]</sup> Furthermore, using a crude-rate analysis method, a significantly greater proportion of dexlansoprazole MR than lansoprazole recipients achieved complete healing of erosive oesophagitis at week 8 in study 1 (85% vs 79%;  $p < 0.05$ ), but not in study 2 (87% vs

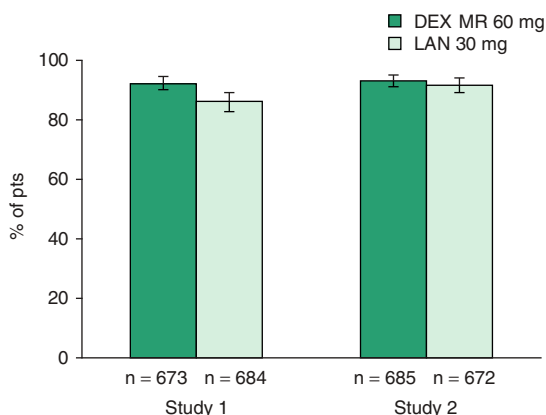
85%).<sup>[24]</sup> In both studies, week 4 healing rates were  $>64\%$  with both treatments by both life-table and crude-rate analysis, with no significant between-group differences.<sup>[24]</sup>

- After 8 weeks' treatment, dexlansoprazole MR 60 mg once daily was more effective than lansoprazole 30 mg once daily in achieving complete healing of more severe grades of erosive oesophagitis in one of the two studies.<sup>[24]</sup> Complete healing was achieved by a significantly greater proportion of patients with LA grade C or D erosive oesophagitis at baseline in the dexlansoprazole MR than in the lansoprazole treatment group by both life-table (89% vs 75%;  $p < 0.05$ ) and crude-rate (80% vs 65%;  $p < 0.05$ ) analysis in study 1, but not in study 2 (88% vs 88% and 78% vs 79%, respectively).<sup>[24]</sup>

- Treatment with once-daily dexlansoprazole MR 30 mg was significantly more effective than that with placebo in maintaining healed erosive-oesophagitis in the overall ITT population (i.e. patients with all grades of erosive oesophagitis at baseline), as assessed using life-table analysis (75% vs 27%;  $p < 0.00001$ ) [primary efficacy analysis].<sup>[25]</sup> Using crude-rate analysis, 66% of dexlansoprazole MR versus 14% of placebo recipients maintained healing at 6 months ( $p < 0.00001$ ).<sup>[25]</sup>

- In patients with LA grade C or D erosive oesophagitis at baseline, the estimated cumulative rate of maintained healing at 6 months using life-table analysis was significantly higher in dexlansoprazole MR than in placebo recipients (63% vs 15%;  $p < 0.0025$ ).<sup>[25]</sup> Similar results were observed using the crude-rate analysis (data not reported).<sup>[25]</sup>

- Furthermore, during the entire treatment period, symptom control was significantly greater in recipients of dexlansoprazole MR 30 mg than in recipients of placebo.<sup>[25]</sup> The median percentage of 24-hour heartburn-free days was 96% versus 29% and nights without heartburn was 99% versus 72% ( $p < 0.0025$  for both).<sup>[25]</sup>



**Fig. 1.** Therapeutic efficacy of dexlansoprazole modified release (DEX MR) in adult (aged  $\geq 18$  years) patients (pts) with all grades of endoscopically proven erosive oesophagitis. The proportion of intent-to-treat pts with complete healing of erosive oesophagitis following 8 weeks' treatment with DEX MR 60 mg or lansoprazole (LAN) 30 mg once daily (primary endpoint), as assessed using life-table analysis, in two randomized, double-blind, multicentre, phase III trials.<sup>[24]</sup> Error bars represent 95% confidence intervals (CIs). Noninferiority of DEX MR 60 mg to LAN 30 mg was achieved as the lower bound of the 95% CI was greater than  $-10$ .

#### Non-Erosive Reflux Disease (NERD)

The symptomatic improvement of heartburn was evaluated in a phase III trial in adult patients with NERD ( $n = 947$ ).<sup>[13]</sup> Patients with endoscopically proven normal oesophageal mucosa



and heartburn as a primary symptom, a history of heartburn episodes for  $\geq 6$  months or experiencing heartburn on  $\geq 4$  out of 7 days preceding randomization were eligible to receive 4 weeks' treatment with dexlansoprazole MR 30 mg ( $n = 315$ ) or 60 mg ( $n = 315$ ), or placebo ( $n = 317$ ) once daily. Dexlansoprazole MR 60 mg once daily is not an approved dosage for the treatment of symptomatic NERD (section 5) and, therefore, these data are not discussed further.<sup>[16]</sup>

Exclusion criteria included pregnancy, breastfeeding, coexisting diseases of the oesophagus, active gastric or duodenal ulcers, use of other PPIs,  $H_2$ -receptor agonists, antacids, anticholinergics, sucralfate or prokinetic agents, or NSAIDs, clinically significant laboratory abnormalities or uncontrolled systemic disease. However, patients were eligible regardless of *H. pylori* status.<sup>[13]</sup>

The primary endpoint was the percentage of 24-hour heartburn-free days (i.e. days with neither daytime nor night-time heartburn) over the 4-week treatment period, as assessed by the patient using a daily electronic diary.<sup>[13]</sup> The percentage of heartburn-free nights was defined as a secondary endpoint.<sup>[13]</sup> Patients rated the presence and severity of heartburn twice daily using a five-point scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe.<sup>[13]</sup> The median mean severity of heartburn at baseline ranged from 1.57 to 1.60 for patients with daytime heartburn and from 1.21 to 1.36 for those with daytime/night-time heartburn. All randomized patients who received at least one dose of study medication and completed the diary on at least 1 day during treatment were included in the modified ITT efficacy analyses; days where the diary data were missing were excluded.<sup>[13]</sup>

- Dexlansoprazole MR treatment provided more effective relief from heartburn than placebo in patients with NERD.<sup>[13]</sup> The median percentage of 24-hour heartburn-free days over a 4-week treatment period (primary endpoint) was significantly greater with once-daily dexlansoprazole MR 30 mg than with placebo (55% vs 19%;  $p < 0.00001$ ).<sup>[13]</sup> Similarly, the median percentage of heartburn-free nights was also significantly greater in the dexlansoprazole MR than in the placebo group (81% vs 52%;  $p < 0.00001$ ).<sup>[13]</sup>

- The severity of heartburn was also reduced to a significantly greater extent with dexlansoprazole MR than with placebo in this study.<sup>[13]</sup> The mean severity scores of heartburn were significantly ( $p < 0.00001$ ) lower in the dexlansoprazole MR 30 mg than in placebo group for daytime (0.74 vs 1.15), night-time (0.56 vs 0.90) and daytime/night-time heartburn (0.66 vs 1.04).<sup>[13]</sup> Furthermore, the corresponding median proportion of days with patients not experiencing daytime heartburn was significantly greater in recipients of dexlansoprazole MR (63% vs 27%;  $p < 0.00001$ ).<sup>[13]</sup>
- A once-daily regimen of dexlansoprazole MR 30 mg provided prompt and sustained relief from heartburn.<sup>[13]</sup> Over the first 3 days of treatment, a significantly greater proportion of dexlansoprazole MR than placebo recipients experienced 24-hour heartburn-free days (14% vs 2%;  $p < 0.00001$ ).<sup>[13]</sup> Furthermore, a significantly greater proportion of dexlansoprazole MR recipients achieved a sustained resolution of heartburn at the end of treatment (59% vs 14% in the placebo group;  $p < 0.00001$ ).<sup>[13]</sup>

#### 4. Tolerability

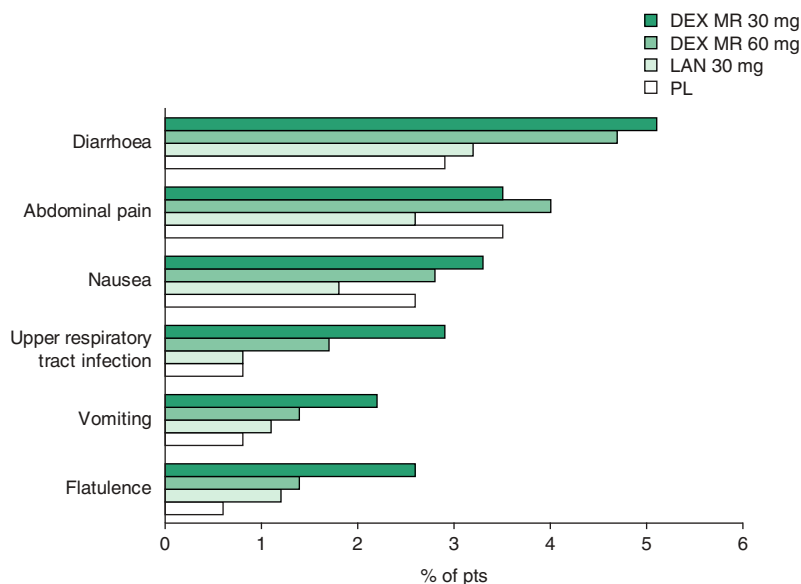
The tolerability profile of oral dexlansoprazole MR 30 and 60 mg once daily was evaluated in the clinical trials in adult patients with erosive oesophagitis<sup>[24,25]</sup> or NERD<sup>[13]</sup> discussed in section 3. This section focuses on tolerability data from these clinical trials and pooled analyses of controlled and/or uncontrolled clinical trials, which are reported in the manufacturer's prescribing information.<sup>[16]</sup> Tolerability data from a further pooled analysis ( $n = 4270$ ), which included a dexlansoprazole MR 90 mg once-daily treatment group (this dosage is not approved),<sup>[18]</sup> are also discussed briefly.

- Dexlansoprazole MR was generally well tolerated in adult patients with erosive oesophagitis or NERD.<sup>[13,18,24,25]</sup> In the descriptive pooled analysis of controlled studies, the most frequent treatment-emergent adverse events (incidence  $\geq 2\%$ ) that occurred with a numerically higher frequency in the dexlansoprazole MR than in the placebo group were diarrhoea, abdominal pain, nausea, upper respiratory tract infection, vomiting and flatulence (figure 2).<sup>[16]</sup>

- The number of patients experiencing at least one treatment-emergent adverse event per 100 patient-months of exposure was 15.64–18.75 in the dexlansoprazole MR treatment arms, 21.06 in the lansoprazole group and 24.49 in the placebo group.<sup>[18]</sup>
- Significantly ( $p < 0.05$ ) fewer recipients of once-daily dexlansoprazole MR 30 or 60 mg than recipients of placebo discontinued treatment because of an adverse event (0.96 and 1.48 vs 3.86 adverse events per 100 patient-months of exposure led to premature discontinuation).<sup>[18]</sup>
- In patients with erosive oesophagitis, the nature and incidence of treatment-emergent adverse events in recipients of dexlansoprazole MR 60 mg once daily broadly resembles that in lansoprazole recipients after 8 weeks' treatment.<sup>[24]</sup> The respective proportion of patients experiencing at least one treatment-emergent adverse event was 30% and 28%.<sup>[24]</sup> There were no treatment-emergent adverse events occurring with a frequency of  $\geq 5\%$  in any treatment arm and the most common adverse event leading to discontinuation of treat-

ment was diarrhoea in recipients of dexlansoprazole MR or lansoprazole.<sup>[24]</sup>

- With short-term treatment (4 weeks), the incidence of treatment-emergent adverse events was not significantly different between recipients of dexlansoprazole MR 30 mg and placebo once daily.<sup>[13]</sup> Diarrhoea, headache, nausea and vomiting were the most frequently reported adverse events.<sup>[13]</sup> Longer-term treatment ( $\leq 6$  months) with dexlansoprazole MR 30 mg once daily was associated with a significantly higher incidence of upper respiratory tract infection than that with placebo (2.2 vs 0.4 per 100 patient-months of exposure;  $p < 0.05$ ).<sup>[25]</sup>
- There were no clinically significant laboratory abnormalities reported in recipients of dexlansoprazole MR 30 or 60 mg once daily in patients with erosive oesophagitis or NERD.<sup>[13,24,25]</sup>
- The FDA has warned of a potential for fracture risk associated with high-dose, long-term use of PPIs.<sup>[26]</sup> In clinical trials to date, no increased incidence of fracture has been observed following dexlansoprazole MR treatment.<sup>[13,24,25]</sup>



**Fig. 2.** Tolerability profile of oral dexlansoprazole modified release (DEX MR). Most frequent (incidence  $\geq 2\%$ ) treatment-emergent adverse events that occurred with a numerically greater frequency in recipients of DEX MR than in placebo (PL) recipients.<sup>[16]</sup> Descriptive pooled data from six randomized, controlled, clinical trials in patients (pts) treated for erosive oesophagitis, maintenance of healed erosive oesophagitis or non-erosive reflux disease. Pts received DEX MR 30 mg ( $n = 455$ ) or 60 mg ( $n = 2218$ ), lansoprazole (LAN) 30 mg ( $n = 1363$ ) or PL ( $n = 896$ ) once daily.

- The FDA has also warned of a drug interaction between omeprazole and clopidogrel that results in a reduced exposure to clopidogrel (see section 2).<sup>[27]</sup> Dexlansoprazole is not expected to affect the pharmacokinetics of clopidogrel.

## 5. Dosage and Administration

In the US, treatment with dexlansoprazole MR 60 mg once daily for up to 8 weeks is recommended for the healing of erosive oesophagitis.<sup>[16]</sup> The recommended dosage is 30 mg once daily for up to 6 months for the maintenance of healed erosive oesophagitis.<sup>[16]</sup> For the management of symptomatic NERD, the recommended dosage is 30 mg once daily for 4 weeks.<sup>[16]</sup> Local prescribing information should be consulted for other contraindications, warnings or recommendations.

## 6. Dexlansoprazole Modified Release: Current Status in Erosive Oesophagitis and NERD

Dexlansoprazole MR is approved in the US for the healing of all grades of erosive oesophagitis, the maintenance of healed erosive oesophagitis and the management of symptomatic NERD in adult patients.<sup>[16]</sup> In large, well designed phase III trials, dexlansoprazole MR treatment provided beneficial effects in terms of achieving complete healing of all grades of erosive oesophagitis after 8 weeks, with these benefits maintained during 6 months of maintenance treatment. In addition, patients with NERD experienced a significant improvement in the proportion of 24-hour heartburn-free days following treatment with dexlansoprazole MR for 4 weeks in a large phase III trial. Dexlansoprazole MR was generally well tolerated in these patient populations in clinical trials of up to 12 months' duration.

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