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"Efficacy and Safety of Dexlansoprazole: A Comprehensive Review"

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Abstract

Gastroesophageal reflux disease (GERD) remains prevalent in medical practice. Proton pump inhibitors (PPIs) are the primary treatment, yet limitations exist. Dexlansoprazole modified release (MR), an R-enantiomer of lansoprazole, offers high efficacy. Its dual release in the duodenum and small intestine yields two peak concentrations at different times (2- and 5-hours post-administration), ensuring the longest maintenance of drug concentration and proton pump inhibitory effect among all PPIs. Dexlansoprazole MR effectively heals erosive esophagitis, maintains healed esophageal mucosa, and controls NERD symptoms. It also improves nocturnal heartburn, GERD-related sleep disturbances, and bothersome regurgitation. Importantly, it maintains good plasma concentration regardless of food intake, enabling flexible dosing. Furthermore, it does not significantly affect clopidogrel metabolism or platelet inhibition, eliminating the need for dose adjustments when co-prescribed. This review highlights dexlansoprazole's unique attributes, pharmacokinetics, advantages, and safety in comparison to traditional PPIs.

Categories: Gastroenterology
Keywords: non-erosive reflux disease, dual delayed released, erosive esophagitis, proton pump inhibitors, dexlansoprazole, gastroesophageal reflux disease

Introduction And Background

Gastro-oesophageal reflux disease (GERD), a medical ailment marked by anomalous backflow of stomach contents into the esophagus, is a widespread clinical condition [1,2]. Common presentations of GERD include symptoms such as pyrosis (heartburn), epigastric discomfort, and regurgitation. These exhibit prevalence rates of approximately 10-20% within the populace of Western nations. Particularly noteworthy is the occurrence of GERD symptoms on a weekly basis among 15-20% of individuals in the United States [3-6]. In Asian regions, GERD's occurrence varies from 6.3% to 18.3%, signifying an escalating tendency relative to earlier reports [7]. GERD can be stratified into two categories: erosive oesophagitis (EO) and non-erosive reflux disease (NERD), with NERD constituting 70% of instances and EO accounting for the remaining 30% [8].

Many strategies have been put forth and explored in the pursuit of mucosal healing and relief from pyrosis symptoms in individuals suffering from gastro-oesophageal reflux disease (GERD). These strategies encompass changes in lifestyle and dietary habits, surgical procedures, and pharmaceutical interventions [9,10]. However, lifestyle and dietary modifications have shown limited effectiveness in alleviating symptoms associated with reflux [11]. Surgical interventions offer a cost-effective alternative and are recommended for GERD patients requiring prolonged treatment or those with a history of persistent reflux episodes [12].

In the realm of treatment, pharmaceutical agents stand as the primary approach [9,10]. Currently, drugs that facilitate the suppression of gastric acid, such as sucralfate, antacids, prokinetics, histamine-2 receptor antagonists (H2RAs), and proton pump inhibitors (PPIs), are widely employed. Extensive research has unequivocally established that PPIs are the foremostly prescribed core therapeutic agents for improving erosive lesions and managing symptomatic manifestations [9,13]. The United States Food and Drug Administration (FDA) recommends the use of seven distinct PPIs (Dexlansoprazole 60 mg, Esomeprazole 40 mg and 20 mg, Pantoprazole 40 mg, Lansoprazole 30 mg, Rabeprazole 20 mg, Omeprazole 20 mg) administered over a period of 4 to 8 weeks in cases characterized by erosive oesophagitis [14-19].

Review

Methodology:

Literature Search Strategy

A comprehensive narrative review of the scientific literature was undertaken to methodologically identify pertinent studies, scholarly articles, and information sources pertinent to the pharmacological attributes and clinical utilities of dexlansoprazole. The search was performed across electronic databases including PubMed, MEDLINE, Embase, Scopus, and Google Scholar. The search terms used included "dexlansoprazole," "pharmacology," "mechanism of action," "clinical applications," and related variations. The search was limited to articles published in English up to June 2023.

Study Selection Criteria

Articles were screened for inclusion based on predefined criteria. Studies were eligible for inclusion if they provided information on the pharmacological properties, mechanism of action, clinical trials, and real-world clinical applications of dexlansoprazole. Both preclinical and clinical studies were considered, including randomized controlled trials, observational studies, case reports, and systematic reviews. Studies focusing on other proton pump inhibitors or general gastrointestinal topics were excluded.

Data Extraction and Synthesis

Relevant data were extracted from selected studies and organized into categories, including pharmacology, mechanism of action, clinical trials, and clinical applications. Information regarding dosages, outcomes, adverse effects, and patient populations was extracted where applicable. The findings from individual studies were synthesized to provide a comprehensive overview of the pharmacological and clinical aspects of dexlansoprazole.

Quality Assessment

The eminence of the included studies was evaluated using suitable tools based on the study design. Studies with low methodological quality were acknowledged, and their potential impact on the overall findings was considered during data interpretation.

Data Analysis

The extracted data were analyzed using a thematic approach. Key themes related to the pharmacology, mechanism of action, clinical efficacy, safety profile, and emerging trends of dexlansoprazole were identified and discussed. The synthesis of information aimed to provide a balanced overview of the available evidence while highlighting gaps and areas of uncertainty.

Limitations of methodology

The review acknowledges potential limitations, including publication bias and the exclusion of non-English articles. Additionally, the accuracy of the review is dependent on the quality and reliability of the included studies.

Proton Pump Inhibitors and Clinical Characteristics of Dexlansoprazole:

Proton pump inhibitors (PPIs) operate through an irreversible inhibition of the H+ K+-ATPase enzyme (proton pump), which constitutes the terminal stage in the biosynthesis of gastric acid [20]. For optimal efficacy, substantial concentrations of PPIs must be available when the proton pump is activated [21,22]. It is noteworthy that not all proton pumps remain concurrently active, and approximately 25% of these pumps regenerate on a daily basis [21,22]. Given that PPIs attain their maximal plasma concentration (Cmax) within a span of 2 hours post oral administration and undergo hepatic metabolism, their presence within the physiological milieu becomes progressively limited over time. Through once-daily dosing, systemic exposure to PPIs experiences a gradual decline, and during the latter segments of the 24-hour dosing interval, the plasma may exhibit an absence of circulating PPIs. This temporal pattern enables unhindered, reconstituted, or newly formed proton pumps to resume the process of gastric acid secretion [23]. As a consequence, conventional dosing of PPIs at standard levels, administered once daily, does not confer complete modulation over gastric acid secretion across the entirety of the 24-hour cycle [22,24].

In summation, while variances in the pharmacokinetic profiles and oral absorption rates exist among diverse proton pump inhibitors (PPIs), these dissimilarities do not engender substantial disparities in their capacity to impede acid secretion, as evidenced by pharmacodynamic investigations [25]. Nonetheless, extending the duration of PPI presence within the systemic circulation holds the potential to heighten the efficacy of acid inhibition [26]. Nonetheless, striving for absolute suppression of acid secretion throughout the entire 24-hour temporal domain is aptly deemed an unattainable and undesired objective.

Nevertheless, notwithstanding the merits inherent in extant proton pump inhibitors (PPIs), considerable

unmet therapeutic requisites persist within the domain of gastro-oesophageal reflux disease (GERD) management. Accounts substantiate that approximately 10-15% of adult individuals afflicted with erosive esophagitis retain a measure of esophageal inflammation even subsequent to an 8-week course of PPI intervention. Notably, this cohort of patients is characterized by a baseline status of moderate-to-severe esophageal inflammation, constituting around 25-30% of the entire assemblage of erosive esophagitis instances [8]. Among those patients who effectuate the healing of their erosive esophagitis within an 8-week therapeutic regimen and subsequently embark on maintenance treatment, a substantial subset-ranging from 15-23% among individuals displaying milder inflammation (as defined by Los Angeles grades A and B) to 24-41% in instances with heightened inflammation (grades C and D)-encounter a recurrence of symptoms within a span of 6 months [27].

Furthermore, it warrants attention that a notable proportion-up to 40%-of adult individuals suffering from non-erosive reflux disease (NERD) persist in experiencing symptomatic manifestations despite adherence to once-daily PPI regimens [8]. As a consequence, a notable contingent of both patients (35.4%) and medical practitioners (34.8%) find themselves dissatisfied with the outcomes wrought by PPI therapy [27]. Additionally, the efficacy of PPIs remains circumscribed in regulating atypical or extra oesophageal presentations of GERD, ameliorating postprandial pyrosis, mitigating nocturnal pyrosis, and augmenting acid control within individuals afflicted by Barrett's oesophagus [28]. It is important to underscore that the necessity of PPIs to be administered prior to meals confers a constraint upon the flexibility of therapeutic scheduling.

Within this framework, dexlansoprazole emerges as an exceptional therapeutic agent, notable for its capacity to liberate patients from rigid mealtime constraints and specific drug administration schedules, all while sustaining its therapeutic efficacy independently of these temporal considerations [29-31]. Dexlansoprazole represents the R-enantiomer of lansoprazole, constituting over 80% of the bioavailable compound subsequent to oral dosing [32]. Its metabolic clearance rate is abbreviated, granting it a systemic exposure fivefold greater than the S-enantiomer of lansoprazole [32]. Noteworthy enhancements have been applied to the chemical structure and pharmaceutical formulation of dexlansoprazole, aimed at augmenting its bioavailability, metabolic profile, and proficiency in negating proton pump activity within the parietal cells of the gastric mucosa. Dexlansoprazole harnesses an innovative, adapted dual-release technology as an intrinsic facet of its pharmaceutical design. The active component undergoes release in two distinct phases, each correspondingly activated at different pH thresholds and temporal intervals. The cumulative outcome is the attainment of dual peak plasma concentrations, thereby yielding a total serum dexlansoprazole concentration thrice that of the left-handed enantiomer. Notably, dexlansoprazole exhibits a diminished elimination pace relative to S-lansoprazole, engendering prolonged restraint upon acid secretion. Its AUC (area under the curve) values register magnitudes 3-5 times higher than those ascribed to the racemic amalgamation or the left-handed stereoisomer [24,32,33].

Dexlansoprazole's active ingredient, encapsulated within two distinct granule compositions, undergoes binary release events from a dexlansoprazole capsule, each occurring at divergent pH conditions. Approximately 25% of the total dosage experiences liberation within the proximal duodenal tract, operating at a pH of 5.5, while the remaining 75% undergoes discharge within the distal reaches of the small intestine, characterized by a pH of 6.75 (Figure *1*). This dual-release mechanism engenders the emergence of two discrete peak drug concentrations within the serum: one manifesting 1-2 hours post-administration, and the other materializing 4-5 hours subsequent to dosing. As a result, the modified-release formulation of dexlansoprazole ensures prolonged retention of the therapeutic agent within the bloodstream, concurrently exhibiting a notably potent suppressive influence upon proton pump activity in contrast to alternative available PPIs [24,33,34]. The extended period of plasma exposure ensuing oral administration of dexlansoprazole MR potentially affords the opportunity to inhibit newly activated proton pumps, those that become operative subsequent to the initial effect of PPI administration.

It is widely recognized that conventional proton pump inhibitors (PPIs) formerly necessitated strict adherence to specific temporal intervals. Patients were required to ingest the medication 30-60 minutes prior to a meal, ensuring optimal inhibition of the active (meal-triggered) proton pumps following absorption, hepatic enzymatic processing, and eventual localization at the target site. In contradistinction, dexlansoprazole presents a distinctive advantage by liberating patients from the requirement to strictly adhere to meal timings and designated drug administration schedules, given that its therapeutic efficacy remains unaltered by these variables [29-31]. It is extensively documented that patients frequently encounter difficulties in complying with therapeutic regimens and often fail to observe recommendations that link drug ingestion to meal instances, along with the stipulation of appropriate intervals between dosages. Notably, approximately a mere 40% of patients adhere to PPI dosing instructions, which results in attenuated acid secretion inhibition and contributes to suboptimal treatment outcomes [35,36]. The discernible disparity in therapeutic efficacy is likely attributed to this non-compliance [35,36]. Furthermore, the discernible variance in PPI effectiveness between controlled clinical trials and real-world scenarios is also traceable to the divergence in patient selection procedures within clinical trials, which cannot be directly extrapolated to everyday contexts. An integral determinant affecting the efficacy of conventional proton pump inhibitors lies in the meticulous oversight of drug administration timing during the course of clinical investigations.

Consequently, the treatment's efficacy, as ascertained through controlled clinical investigations, distinctly surpasses its effectiveness in real-world applications. Hence, a noteworthy merit of enhancing patient engagement (compliance) and therapeutic efficacy resides in the fact that the administration of dexlansoprazole subsequent to or before meals, spanning breakfast, lunch, dinner, or an evening snack, does not engender any clinically noteworthy influence upon the regulation of intragastric pH over the course of the entire day (Figure *2*)[31].

A randomized, open-label crossover study was conducted to investigate the effects of administering dexlansoprazole 60 mg at various time points throughout the day in a cohort of 48 healthy participants. Solely the modified-release (MR) formulation of dexlansoprazole was subjected to examination, and alternate dosages were not included in the assessment. The drug was administered once daily for a consecutive span of 5 days, at four distinct time intervals: prior to breakfast, lunch, dinner, and an evening snack [30].

In instances where dexlansoprazole MR was ingested before each meal, there was an observed delay in the drug's absorption, as compared to when it was administered specifically before breakfast. However, this delay in absorption did not result in discernible divergences in the pharmacokinetic profiles of the drug. Metrics such as the maximum plasma concentration (Cmax), the area under the curve (AUC), and the half-life of the drug exhibited consistent characteristics irrespective of the timing of administration. It is pertinent to note a substantial reduction in intragastric pH was observed when the drug was administered before an evening snack in comparison to other time intervals.

Conclusively, dexlansoprazole MR consistently preserves control over intragastric pH levels throughout a 24-hour period, except when it is administered before an evening snack. These findings indicate that dexlansoprazole MR offers heightened dosing flexibility in contrast to other delayed-release PPIs in the context of GERD treatment. This attribute may substantially contribute to enhanced adherence to the prescribed therapeutic regimen.

Dexlansoprazole In the treatment of GERD

It is widely established that a subset of gastro-oesophageal reflux disease (GERD) patients (17-35%) undergoing treatment with omeprazole or alternative proton pump inhibitors (PPIs) continue to exhibit symptoms of the ailment [37-40]. Studies have indicated that up to 35.4% of patients and 34.8% of medical practitioners express dissatisfaction with the outcomes stemming from conventional PPI-based therapeutic interventions [41]. The emergence of resistance to hyposecretory treatment may arise from a multitude of factors. Certain factors are attributed to medical practitioners, encompassing inaccurate diagnoses, inappropriate dosages of medications, or durations of treatment deemed insufficient. Meanwhile, other factors are patient-related, including non-adherence to prescribed regimens or genotypic distinctions that impact drug metabolism. Additionally, drug-associated factors, such as the duration of maintaining gastric pH levels above 4, can contribute to the diminished effectiveness of PPIs in GERD management. Non-acidic reflux episodes or instances of nocturnal acid breakthrough within the gastric environment, coupled with concurrent sleep disorders, may also underlie the inefficacy of PPIs in GERD treatment [42,43]. Further complexity arises from instances of misdiagnosis, wherein GERD is erroneously diagnosed instead of functional heartburn, eosinophilic esophagitis, incipient achalasia of the cardia, autoimmune disorders, or coexisting psychiatric conditions [38,39,41,43,44].

In light of these factors, in addition to validating the correctness of the diagnosis, it is essential to investigate alternative approaches to improve treatment results. These approaches may involve prolonging the treatment duration, adjusting dosage regimens, or considering alternative inhibitors as a replacement. One of the newer alternatives, Dexlansoprazole, deserves special consideration. A comparative study conducted in healthy volunteers sought to evaluate the impact of a single dose of dexlansoprazole 60 mg and esomeprazole 40 mg on average intragastric pH values over a 24-hour period, along with the percentage of time during which pH levels exceeded 4. The study disclosed statistically noteworthy distinctions between the two agents: 4.3 vs. 3.7 ($p = 0.003$) for average pH and 58% vs. 48% ($p < 0.001$) for the proportion of time above pH 4, respectively (see Table *1*) (Figure *3*)[45].

In an indirect comparison, esomeprazole 40 mg exhibited prolonged durations of intragastric acid suppression, maintaining pH levels above 4, when juxtaposed with standard doses of pantoprazole, lansoprazole, rabeprazole, and omeprazole [46-48]. Moreover, it showcased more sustained acid control relative to low-dose esomeprazole in GERD-afflicted patients. Nevertheless, dexlansoprazole 60 mg demonstrated elevated intragastric pH levels and displayed a substantial temporal difference in acid control durations compared to esomeprazole 40 mg within a healthy subject cohort [45].

A double-blind, placebo-controlled trial was conducted to assess the efficacy and safety of dexlansoprazole MR in managing symptoms among patients with non-erosive reflux disease (NERD), spanning a 4-week duration (see Table *1*) [49]. The trial encompassed 947 NERD patients, randomly assigned to receive once-daily dosages of either dexlansoprazole MR 30 mg, dexlansoprazole MR 60 mg, or placebo. All enrolled patients experienced heartburn for at least 6 months and exhibited normal esophageal mucosa upon upper

endoscopy. During a 7-day run-in period, patients were required to encounter heartburn symptoms for a minimum of 4 days. The outcomes demonstrated that both dexlansoprazole MR 30 mg and 60 mg led to markedly higher median percentages of heartburn-free days over a 24-hour period compared to placebo (54.9% and 50.0% vs. 17%, respectively; $p < 0.00001$). Moreover, patients receiving dexlansoprazole MR 60 mg and 30 mg experienced significantly greater proportions of nights devoid of heartburn relative to those given placebo (80.8% and 76.9% vs. 51.7%, respectively; $p < 0.00001$) [49].

The relief of heartburn was evident as early as the third day of dexlansoprazole MR treatment and was sustained throughout the 4-week treatment period. An indirect comparison of randomized controlled trials, juxtaposing dexlansoprazole MR with esomeprazole, revealed that at 4 weeks, dexlansoprazole MR 30 mg exhibited superior effectiveness in controlling heartburn symptoms in NERD patients compared to esomeprazole 20 mg or 40 mg (risk ratio: 2.01, 95% confidence interval: 1.15-3.51; risk ratio: 2.17, 95% confidence interval: 1.39-3.38, respectively) (refer to Table *1*) [50].

Within this comparative study, the baseline acid regurgitation score was higher in the esomeprazole group than in the dexlansoprazole group (3.3±0.6 vs. 3.0±0.5; P=0.011). Notably, acid reflux sensation constitutes just one facet of GERD clinical symptoms, and no statistically significant differences were observed in scores for heartburn and epigastric acidity between the two groups. The utilization of the GERDQ score, a comprehensive six-item questionnaire, provides a more objective approach for diagnosing and evaluating GERD treatment efficacy compared to a single item [51,52]. Baseline GERDQ scores for both groups exhibited no significant difference (23.2±3.7 vs. 23.7±4.7; P=0.878). After completing the initial 8-week therapy, patients transitioned to on-demand treatment for the subsequent study duration. The overall complete symptom resolution (CSR) rates and improvements in the GERDQ score were comparable between the two groups. However, over a 24-week period, dexlansoprazole demonstrated fewer days with reflux symptoms compared to esomeprazole (53.9±54.2 vs. 37.3±37.8; P=0.008).

Additionally, it was observed that the dexlansoprazole group displayed sustained enhancements in the GERDQ score during the on-demand period (week 8 vs. week 24; P<0.001), whereas no such continuous improvement was observed in the esomeprazole group (week 8 vs. week 24; P=0.846). This suggests potential divergent durations of drug retention in the bloodstream between these potent PPIs. In a one-week comparative study, 40 mg esomeprazole necessitated more time (3 days) to achieve complete symptom resolution (CSR) in comparison to 60 mg dexlansoprazole, particularly among females due to the influence of oestrogen and progesterone on lower esophageal sphincter relaxation [53-55].

Notably, dexlansoprazole does not exhibit an accumulation effect with multiple once-daily doses of 60 mg. On day 5, maximum concentration (Cmax) values of dexlansoprazole were slightly higher (<10%) in comparison to day 1 [33,56]. Consequently, dexlansoprazole can achieve desired concentrations almost immediately. In a one-day pH study conducted 12-24 hours post-dose, an assessment of pharmacokinetic effects among different PPIs indicated that dexlansoprazole exhibited a higher mean percentage of time with pH > 4 and an elevated average mean pH compared to esomeprazole (60% vs. 42%, P<0.001 and 4.5 vs. 3.5, P<0.001, respectively) [45]. However, this study did not provide insights into the clinical effects of tablet usage. Fass et al. reported that 84% of patients previously administered twice-daily esomeprazole achieved well-controlled heartburn symptoms upon transitioning to once-daily dexlansoprazole for maintenance [57]. These patients managed to maintain the severity of their GERD-related symptoms and quality of life, evident by marginal changes in the PAGISYM and PAGI-QOL total and subscale scores, respectively. This study observed a trend indicating that there were fewer dexlansoprazole tablets used in comparison to esomeprazole (91.3±40.2 vs. 96.7±44.9) and lower GERDQ scores at 16, 20, and 24 weeks during on-demand treatment in the dexlansoprazole group as opposed to the esomeprazole group {14.7±4.4 vs. 16.2±4.7 (P=0.365), 13.7±3.2 vs. 15.0±4.8 (P=0.124), and 13.1±3.8 vs. 16.5±10.9 (P=0.252), respectively}, although statistical significance was not reached. This could potentially be attributed to the relatively small sample size of the study. Consequently, dexlansoprazole may present as a more optimal once-daily PPI option for on-demand use when compared to esomeprazole.

Drug Interactions:

When considering the utilization of dexlansoprazole inpatient treatment regimens, clinicians must carefully evaluate the potential for interactions with concurrently administered medications. The metabolism of dexlansoprazole primarily takes place within the liver, involving intricate processes such as oxidation, reduction, and conjugation with entities like sulphates, glucuronate, and glutathione. These transformations lead to the formation of metabolites devoid of activity. The cytochrome P450 (CYP) enzyme system, notably CYP2C19 and CYP3A4, plays a significant role in generating oxidation metabolites, including hydroxy dexlansoprazole and its glucuronate. In individuals exhibiting moderate to extensive CYP2C19 metabolism, 5-hydroxy dexlansoprazole and its glucuronate predominate, while those with diminished CYP2C19 metabolism showcase the sulphonic metabolite as the principal plasma derivative [8,10,11,33]. Co-administration of medications capable of inhibiting the CYP2C19 enzyme (e.g., fluvoxamine) can elevate the systemic exposure to dexlansoprazole. Conversely, drugs inducing CYP2C19 and CYP3A4 activity (such as rifampicin and St. John's wort extract) may diminish the plasma concentration of dexlansoprazole [34, 58].

Analogous to other proton pump inhibitors, dexlansoprazole carries the potential to impede the absorption of drugs influenced by gastric juice pH. Hence, its concurrent use with atazanavir and nelfinavir, leading to diminished systemic exposure to these drugs, should be avoided. Similarly, dexlansoprazole pH-dependent effects can interfere with the absorption of ketoconazole, itraconazole, and erlotinib, warranting caution in their concomitant administration. However, dexlansoprazole exhibits negligible effects on the pharmacokinetics of phenytoin, theophylline, or diazepam. Contrastingly, combining dexlansoprazole with digoxin or tacrolimus may elevate their plasma concentrations. Consequently, vigilant monitoring of drug levels upon initiating and concluding therapy, coupled with dosage adjustments, if necessary, is prudent. Notably, transplant recipients displaying moderate or slow metabolism involving CYP2C19, considering that tacrolimus is a CYP3A4 substrate, should exercise particular care in this context [34,58].

A noteworthy attribute of dexlansoprazole lies in its lack of clinically substantial pharmacokinetic interactions with thienopyridine derivatives, particularly clopidogrel. Hence, no dosage modification is required when concurrently administering these drugs at approved doses [58-60]. A subgroup meta-analysis by Niu et al. in 2017 determined that co-administration of clopidogrel with omeprazole, lansoprazole, esomeprazole, or pantoprazole during coronary artery disease management markedly heightened the risk of major cardiovascular events (MACEs) [61]. Under such circumstances, dexlansoprazole emerges as a preferred option to avert these interactions. The FDA has also elucidated the concomitant use of clopidogrel (Plavix; Bristol-Myers Squibb, New York, NY, USA): "Avoid concurrent use of Plavix with omeprazole or esomeprazole because both significantly reduce the antiplatelet activity of Plavix" [33]. This assertion is corroborated by the Plavix Full Prescribing Information, affirming that dexlansoprazole, lansoprazole, and pantoprazole exert a milder impact on Plavix's antiplatelet activity in comparison to omeprazole or esomeprazole [62,63].

Safety:

Based on extensive clinical investigations involving a cohort of over 4,500 patients, spanning across seven distinct clinical trials, dexlansoprazole has exhibited a commendable safety profile, characterized by infrequent occurrences of adverse reactions that seldom warrant the cessation of treatment. The safety of orally administered dexlansoprazole at dosages of 30 mg, 60 mg, and 90 mg has been rigorously examined through year-long clinical trials. The reported instances of adverse drug reactions were predominantly of mild or moderate intensity, with their incidence either comparable to or lower than those noted for the placebo or lansoprazole comparator. Among the frequently reported adverse effects were diarrhoea (leading to discontinuation in 0.7% of instances), abdominal pain, headache, nausea, abdominal discomfort, flatulence, and constipation [58,64,65].

In consonance with the behaviour of other proton pump inhibitors (PPIs), levels of gastrin manifest an over twofold increase during the initial three months of dexlansoprazole therapy, subsequently stabilizing without any discernible clinical or morphological repercussions. The enduring efficacy of prolonged treatment, in terms of effectively managing reflux symptoms and enhancing the patient’s quality of life, is upheld throughout the duration of maintenance therapy, as reaffirmed through a one-year follow-up study [64,66].

Limitation of conventional PPI and how does Dexlansoprazole address it?

Conventional proton pump inhibitors (PPIs) are widely used medications for the treatment of gastroesophageal reflux disease (GERD) and other acid-related disorders. However, they do have certain limitations. Dexlansoprazole is a modified-release formulation of PPI that aims to address some of these limitations.

One limitation of conventional PPIs is their short half-life, which can result in incomplete acid suppression and symptom recurrence between doses. This limitation is discussed by Metz DC et al., in their article [56]. The article explains that dexlansoprazole, through its modified-release formulation, offers an extended duration of acid suppression compared to conventional PPIs [56,67].

Another limitation of conventional PPIs is their dependence on meal timing. To achieve optimal efficacy, conventional PPIs need to be taken before meals, which can be inconvenient for some patients and may result in reduced adherence to therapy [56,64,67]. This limitation is addressed by Peura et al. in their study titled "Dexlansoprazole MR Versus Placebo and Lansoprazole to Assess Meal-Triggered Symptom Relief in Patients With GERD" published in The American Journal of Gastroenterology in 2009 [64]. The study demonstrates that dexlansoprazole can provide effective and sustained acid control regardless of meal timing, making it more convenient for patients [64,67].

Furthermore, conventional PPIs may exhibit interindividual variability in their pharmacokinetics and pharmacodynamics, which can affect their effectiveness. The article by Metz DC et al., also highlights that dexlansoprazole demonstrates consistent plasma levels and acid suppression across a range of doses, minimizing interpatient variability and providing predictable therapeutic outcomes [56,66]. In summary, dexlansoprazole, as a modified-release formulation of PPI, addresses the limitations of conventional PPIs by

offering extended acid suppression, providing flexibility in meal timing, and reducing interindividual variability. These advantages are supported by the studies mentioned above. According to the ACG Guideline, Dexlansoprazole has better control of intragastric pH regardless of meal timing [68].

Author, year	Study Design and sample size	Study drugs and sample size	Outcome
GERD, ERD			
Lee RD et al. [30] 2007	Open-label, single-dose, randomized, 4-way crossover study, N=48	Dexlansoprazole MR 90 mg	In the majority of patients, dexlansoprazole MR can be administered without considering meals or their timing.
Kukulka M et al. [45] 2011	a single-center, Phase – 1, open-label, randomized, two-period crossover study, N=87	60 mg of Dexlansoprazole with a dual delayed release mechanism, 40 mg of Esomeprazole with dual delayed release.	In healthy subjects, Dexlansoprazole 60mg exhibited elevated intragastric pH levels and a notable distinction in the duration of acid control compared to Esomeprazole 40mg.
Fass R et al. [49] 2009	Double blind RCT, N=947	Dexlansoprazole MR 30 mg, 60 mg Vs. Placebo	In patients with nonerosive reflux disease (NERD), both Dexlansoprazole MR 30 mg and 60 mg showed superiority over placebo by offering a higher number of heartburn-free days and nights over a 24-hour period. The treatment was well tolerated.
Wu MS et al. [50] 2013	Conduct a systematic review of an indirect comparison study between dexlansoprazole and esomeprazole in the context of GERD..	Dexlansoprazole 30 mg, Esomeprazole 20 mg/40mg	Patients undergoing treatment with dexlansoprazole 30 mg would experience a notably greater and statistically significant improvement in symptom control compared to those receiving esomeprazole 20 mg or 40 mg in the 4-week management period.
Katz PO et al., [68] 2022	ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease	All PPI	Dexlansoprazole, a dual delayed release PPI, in which first absorption is in the duodenum, then partially further down the small bowel, seems to have similar efficacy in pH control regardless of meal timing.
Li et al. [69] 2017	PRISMA Compliant Meta-analysis, N = 25,088	Dexlansoprazole (60 mg) Pantoprazole (40 mg) Esomeprazole (40 mg) Lansoprazole (30 mg) Esomeprazole (20 mg) Rabeprazole (20 mg) Omeprazole (20 mg)	Utilizing data from the dexlansoprazole 60mg trial, it appears that esomeprazole 40mg exhibited the highest likelihood of achieving mucosal healing at 4 weeks, with a probability of 98%.
Sharma P et al. [70] 2009	RCT, N=4092	Dexlansoprazole MR 60/90, Lansoprazole 30 mg	The efficacy of Dexlansoprazole MR in healing erosive oesophagitis (EO) is substantial, providing advantages over lansoprazole, particularly in cases of moderate-to-severe disease.
Emerson CR et al. [71] 2010	Review article of Literature	Dexlansoprazole 30, 60, and 90 mg,	Dexlansoprazole demonstrated favorable tolerance and effectiveness in both healing and maintaining erosive esophagitis (EE) as well as treating nonerosive reflux disease.
Dumra H et al., [72] 2023	Expert recommendation, Review article	All PPI,	Amongst the various PPIs available, dexlansoprazole is recommended for patients with nocturnal symptoms due to its 24-hour acid-control action. In the LA 3 and 4 subgroups, esomeprazole is favoured over other PPIs, despite its high cost.

TABLE 1: Summary of some important studies of Dexlansoprazole.

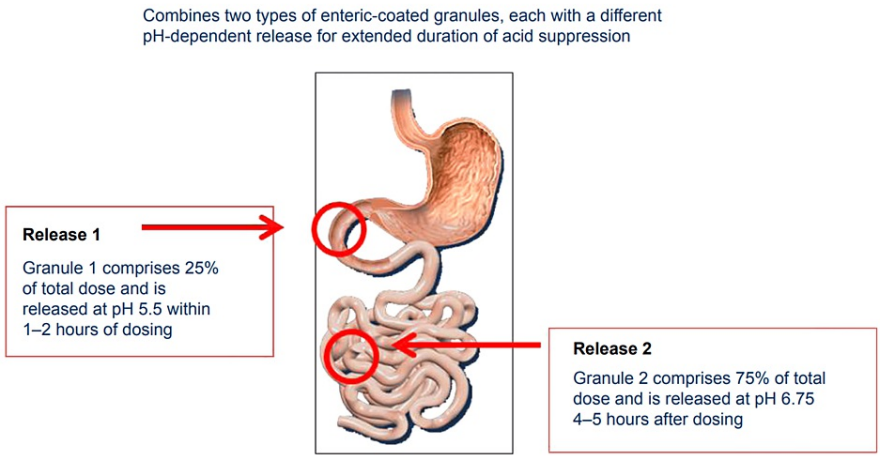

FIGURE 1: The dual delayed-release mechanism of dexlansoprazole facilitates the sequential release of the drug in two distinct phases.

[33]

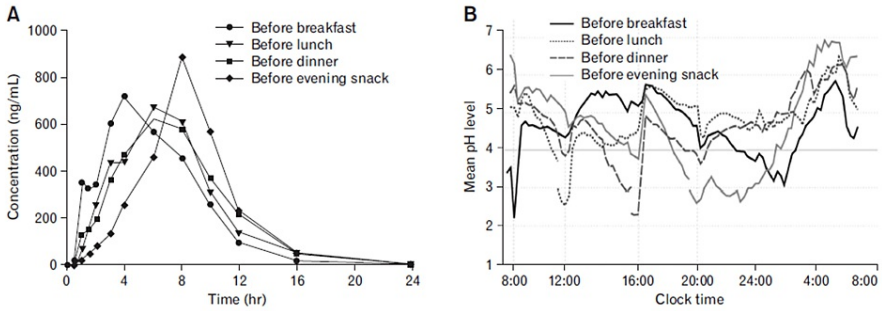

FIGURE 2: Results obtained on the fifth day subsequent to daily oral administrations of dexlansoprazole at a dosage of 60 mg, administered 30 minutes before meals or an evening snack, are depicted

Panel (A) showcases the average linear plasma concentration-time profiles, while Panel (B) exhibits the average intragastric pH measurements. In the context of the 24-hour temporal scale, the x-axis delineates the interval spanning from 8:00 AM on the morning of day 5 to 8:00 AM on day 6. The commencement and cessation of monitoring periods for each respective regimen are indicated by upward and downward-pointing arrows, respectively. For the lunch, dinner, and snack regimens, data post 8:00 AM on day 6 have been transposed to the initial segment of the graphical representation. This alignment facilitates the juxtaposition of the mean 24-hour pH profiles of all four distinct regimens within a unified 24-hour visualization, thereby affording insight into the diurnal influence of treatment on pH levels [31].

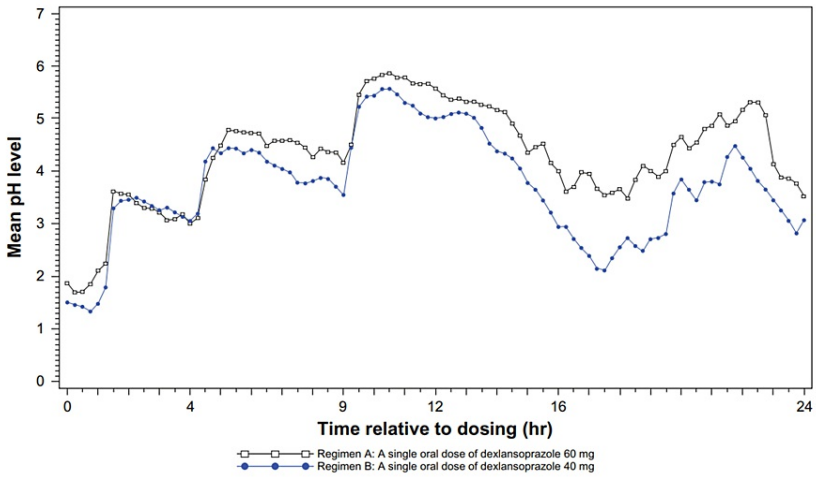

FIGURE 3: Average intragastric pH levels spanning the interval from 0 to 24 hours subsequent to the administration of individual oral doses of dexlansoprazole in a modified-release formulation at 60 mg (n = 43), and esomeprazole in delayed-release capsules at 40 mg (n = 44), were evaluated.

[45]

Conclusions

Dexlansoprazole, an advanced proton pump inhibitor of the next generation, signifies a notable breakthrough in the management of conditions associated with gastric hydrochloric acid, specifically diverse manifestations of gastroesophageal reflux disease (GERD). Dexlansoprazole holds the potential to offer distinctive advantages, particularly to patients afflicted with nocturnal reflux and sleep disturbances attributed to GERD, due to its 24-hour acid-control action. Moreover, this pharmaceutical agent exhibits remarkable efficacy in both the therapeutic healing of erosive esophagitis lesions caused by reflux and the sustained maintenance of their remission. As an enantiomer of lansoprazole with a dextrorotatory orientation, dexlansoprazole surpasses its counterparts in its capability to curtail the production of gastric acid. A defining characteristic that sets dexlansoprazole apart is its utilization of an innovative controlled-release mechanism, ensuring a continuous presence of the therapeutic agent within the systemic circulation, thereby leading to an extended duration of proton pump inhibition. A notable aspect is that the efficacy of dexlansoprazole remains unaffected by meal timing, thereby facilitating enhanced adherence and cooperation among patients in their daily clinical routines. The drug's attributes encompass a favorable safety profile and minimal likelihood of precipitating adverse interactions with concurrent medications. Dexlansoprazole effectively meets unaddressed therapeutic requirements in the context of gastroesophageal reflux disease, thus signifying a notable stride in clinical management.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** Dr Dinesh Patil, Dr Onkar Swami declare(s) employment from Alembic Pharmaceuticals. Bothe the above mentioned authors are permanent employee of the Alembic Pharmaceutical, Mumbai, Maharashtra, India. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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