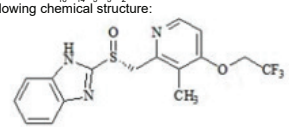
KAPDEX™
(Dexlansoprazole)

کیپ ڈیکس

QUALITATIVE AND QUANTITATIVE COMPOSITION
KAPDEX Capsules 30 mg
Each delayed-release capsule contains:
Dexlansoprazole (dual delayed-release pellets).....30 mg
KAPDEX Capsules 60 mg
Each delayed-release capsule contains:
Dexlansoprazole (dual delayed-release pellets).....60 mg

DESCRIPTION
The active ingredient in KAPDEX is Dexlansoprazole, a proton pump inhibitor. Chemically, it is (+)-2-[(R)-{[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl] methyl} sulfinyl]-1H-benzimidazole, a compound that inhibits gastric acid secretion. Dexlansoprazole is the R-enantiomer of lansoprazole (a racemic mixture of the R- and S-enantiomers). Its empirical formula is $C_{16}H_{14}F_3N_3O_2S$, with a molecular weight of 369.36. Dexlansoprazole has the following chemical structure:



CLINICAL INFORMATION
Indications
Healing of erosive esophagitis
KAPDEX (Dexlansoprazole) is indicated in patients 12 years of age and older for healing of all grades of erosive esophagitis (EE) for up to eight weeks.
Maintenance of Healed Erosive Esophagitis and Relief of Heartburn
KAPDEX (Dexlansoprazole) is indicated in patients 12 years of age and older to maintain healing of EE and relief of heartburn for up to six months in adults and 16 weeks in patients 12 to 17 years of age.
Treatment of symptomatic non-erosive gastroesophageal reflux disease
KAPDEX (Dexlansoprazole) is indicated in patients 12 years of age and older for the treatment of heartburn associated with Symptomatic non-erosive gastroesophageal reflux disease (GERD) for four weeks.

Dosage and Administration
Adult Dosage

Table 1: Recommended KAPDEX Capsules Dosage Regimen by Indication in Patients 12 Years of Age and Older

Indication	Dosage of KAPDEX Capsules	Duration
Healing of EE	One 60 mg capsule once daily.	Up to 8 weeks
Maintenance of Healed EE and Relief of Heartburn	One 30 mg capsule once daily.	Controlled studies did not extend beyond 6 months in adults and 16 weeks in patients 12 to 17 years of age.
Symptomatic Non-Erosive GERD	One 30 mg capsule once daily.	4 weeks.

Dosage Adjustment
Patients with Hepatic Impairment for the Healing of Erosive Esophagitis
For patients with moderate hepatic impairment (Child-Pugh Class B), the recommended dosage is 30 mg KAPDEX (Dexlansoprazole) once daily for up to eight weeks. KAPDEX (Dexlansoprazole) is not recommended in patients with severe hepatic impairment (Child-Pugh Class C).
Administration Requirement
• Take without regard to food.
• If a dose is missed, administer as soon as possible. However, if the next scheduled dose is due, do not take the missed dose, and take the next dose on time. Do not take two doses at one time to make up for a missed dose.

Contraindications
Dexlansoprazole is contraindicated in
• Patients with known hypersensitivity to any component of the formulation. Hypersensitivity reactions, including anaphylaxis may occur. Acute interstitial nephritis (AIN) may occur with other proton pump inhibitors (PPIs), including lansoprazole of which Dexlansoprazole is the R-enantiomer with rilpivirine-containing products.

Warnings and Precautions
Presence of Gastric Malignancy
In adults, symptomatic response to therapy with Dexlansoprazole does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing in adult patients who have a suboptimal response or an early symptomatic relapse after completing treatment with a PPI. In older patients, also consider an endoscopy.
Acute Interstitial Nephritis
Acute interstitial nephritis may occur in patients taking PPIs including lansoprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue Dexlansoprazole if acute interstitial nephritis develops.
Clostridium difficile-Associated Diarrhea
PPI therapy like Dexlansoprazole may be associated with an increased risk of Clostridium difficile-associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve.
Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.
Bone Fracture
It is known that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the conditions being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines.
Cutaneous and Systemic Lupus Erythematosus
Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) are known to occur in patients taking PPIs. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE.
The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.
Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI-associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.
Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving Dexlansoprazole, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in four to 12 weeks. Serological (e.g., ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.
Cyanocobalamin (Vitamin B12) Deficiency
Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than three years) may lead to malabsorption of cyanocobalamin (Vitamin B12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy are known to occur in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed in patients treated with Dexlansoprazole.
Hypomagnesemia
Hypomagnesemia, symptomatic and asymptomatic, is known to occur rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.
For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), healthcare professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.
Interactions with Investigations for Neuroendocrine Tumors
Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop Dexlansoprazole treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g., for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.
Interaction with Methotrexate
Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients.
Fundic gland polyps
PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPI users who developed fundic gland polyps are asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

Interactions
In the table below drugs with clinically important drug interactions and interaction with diagnostics when administered concomitantly with Dexlansoprazole and instructions for preventing or managing them. Consult the labeling of concomitantly used drugs to obtain further information about interactions with PPIs.

Table 2:
Clinically Relevant Interactions Affecting Drugs Co-Administered with KAPDEX and Interactions with Diagnostics

Antiretrovirals	
Clinical Impact:	The effect of PPIs on antiretroviral drugs is variable. The clinical importance and the mechanisms behind these interactions are not always known. • Decreased exposure of some antiretroviral drugs (e.g., rilpivirine, atazanavir, and nelfinavir) when used concomitantly with dexlansoprazole may reduce antiviral effect and promote the development of drug resistance. • Increased exposure of other antiretroviral drugs (e.g., saquinavir) when used concomitantly with dexlansoprazole may increase toxicity of the antiretroviral drugs. • There are other antiretroviral drugs which do not result in clinically relevant interactions with dexlansoprazole.
Intervention:	Rilpivirine-containing products: Concomitant use with KAPDEX is contraindicated Atazanavir. Nelfinavir: Avoid concomitant use with KAPDEX Saquinavir: Monitor for potential saquinavir toxicities.
Warfarin	
Clinical Impact:	Increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death.

Intervention:	Monitor INR and prothrombin time. Dose adjustment of warfarin may be needed to maintain target INR range.
Methotrexate	
Clinical Impact:	Concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum concentrations of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. No formal drug interaction studies of high-dose methotrexate with PPIs have been conducted
Intervention:	A temporary withdrawal of KAPDEX may be considered in some patients receiving high-dose methotrexate.
Digoxin	
Clinical Impact:	Potential for increased exposure of digoxin.
Intervention:	Monitor digoxin concentrations. Dose adjustment of digoxin may be needed to maintain therapeutic drug concentrations. See prescribing information for digoxin.
Drugs Dependent on Gastric pH for Absorption (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole/itraconazole)	
Clinical Impact:	Dexlansoprazole can reduce the absorption of other drugs due to its effect on reducing intragastric acidity.
Intervention:	Mycophenolate mofetil (MMF): Co-administration of PPIs in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients
Tacrolimus	
Clinical Impact:	Potentially increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.
Intervention:	Monitor tacrolimus whole blood trough concentrations. Dose adjustment of tacrolimus may be needed to maintain therapeutic drug concentrations. See prescribing information for tacrolimus.
Interactions with Investigations of Neuroendocrine Tumors	
Clinical Impact:	CgA levels increase secondary to PPI-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors
Intervention:	Temporarily stop KAPDEX treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g., for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.
Interaction with Secretin Stimulation Test	
Clinical Impact:	Hyper-response in gastrin secretion in response to secretin stimulation test, falsely suggesting gastrinoma.
Intervention:	Temporarily stop KAPDEX treatment at least 30 days before assessing to allow gastrin levels to return to baseline.
False Positive Urine Tests for THC	
Clinical Impact:	There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs.
Intervention:	An alternative confirmatory method should be considered to verify positive results.

Table 3. Clinically Relevant Interactions Affecting KAPDEX When Co-Administered with Other Drugs and Substances

CYP2C19 or CYP3A4 Inducers	
Clinical Impact:	Decreased exposure of dexlansoprazole when used concomitantly with strong inducers.
Intervention:	St. John's Wort, rifampin: Avoid concomitant use with KAPDEX. Ritonavir-containing products.
CYP2C19 or CYP3A4 Inhibitors	
Clinical Impact:	Increased exposure of dexlansoprazole is expected when used concomitantly with strong inhibitors.
Intervention:	Increased exposure of dexlansoprazole is expected when used concomitantly with strong inhibitors.

Pregnancy and breastfeeding
There is no data available with Dexlansoprazole use in pregnant women and fetal risk cannot be ruled out, therefore Dexlansoprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Breastfeeding
It is not known whether Dexlansoprazole is excreted in human milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Adverse Reactions
Serious Adverse Reactions
Acute Interstitial Nephritis, *Clostridium difficile*-Associated Diarrhea, Bone Fracture, Cutaneous and Systemic Lupus Erythematosus, Cyanocobalamin (Vitamin B12) Deficiency and Hypomagnesaemia.
Common Adverse Reactions
Diarrhea, Abdominal Pain, Nausea, Upper, Respiratory Tract Infection, Vomiting and Flatulence.
Adverse Reactions Resulting in Discontinuation
Diarrhea

Overdose
Multiple doses of Dexlansoprazole 120 mg and a single dose of Dexlansoprazole 300 mg does not result in death or other severe adverse events. However, serious adverse events of hypertension are known to occur in association with twice daily doses of Dexlansoprazole 60 mg. Non-serious adverse reactions observed with twice daily doses of Dexlansoprazole 60 mg include hot flashes, contusion, oropharyngeal pain, and weight loss. Dexlansoprazole is not expected to be removed from the circulation by hemodialysis. In the event of over-exposure, treatment should be symptomatic and supportive.

PHARMACOLOGICAL PROPERTIES
Pharmacotherapeutic group: Proton pump inhibitors (ppis)
Mechanism of action
Dexlansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of the (H+, K+)-ATPase at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, Dexlansoprazole is characterized as a gastric proton-pump inhibitor, in that it blocks the final step of acid production.
Pharmacokinetic properties
Absorption
C_{max} and AUC values of Dexlansoprazole increased approximately dose proportionally.
When granules of Dexlansoprazole 60 mg are mixed with water and dosed via NG tube or orally via syringe, the bioavailability (C_{max} and AUC) of Dexlansoprazole was similar to that when Dexlansoprazole 60 mg was administered as an intact capsule
Effect of Food
In food-effect data in healthy subjects receiving Dexlansoprazole under various fed conditions compared to fasting, increases in C_{max} ranged from 12 to 55%, increases in AUC ranged from 9 to 37%, and T_{max} varied (ranging from a decrease of 0.7 hours to an increase of three hours)
Distribution
Plasma protein binding of Dexlansoprazole ranged from 96 to 99% in healthy subjects and was independent of concentration from 0.01 to 20 mcg/mL. The apparent volume of distribution (Vz/F) after multiple doses in symptomatic GERD patients was 40 L.
Metabolism
Dexlansoprazole is extensively metabolized in the liver by oxidation, reduction, and subsequent formation of sulfate, glucuronide and glutathione conjugates to inactive metabolites. Oxidative metabolites are formed by the cytochrome P450 (CYP) enzyme system including hydroxylation mainly by CYP2C19, and oxidation to the sulfone by CYP3A4.
CYP2C19 is a polymorphic liver enzyme which exhibits three phenotypes in the metabolism of CYP2C19
substrates: extensive metabolizers (*1/*1), intermediate metabolizers (*1/mutant) and poor metabolizers (mutant/mutant). Dexlansoprazole is the major circulating component in plasma regardless of CYP2C19 metabolizer status. In CYP2C19 intermediate and extensive metabolizers, the major plasma metabolites are 5-hydroxy dexlansoprazole and its glucuronide conjugate, while in CYP2C19 poor metabolizers Dexlansoprazole sulfone is the major plasma metabolite.
Elimination
Following the administration of Dexlansoprazole, no unchanged dexlansoprazole is excreted in urine. Following the administration of [14C] dexlansoprazole to six healthy male subjects, approximately 50.7% (standard deviation (SD): 9.0%) of the administered radioactivity was excreted in urine and 47.6% (SD: 7.3%) in the feces. Apparent clearance (CL/F) in healthy subjects was 11.4 to 11.6 L/hour, respectively, after five days of 30 or 60 mg once daily administration.

PHARMACEUTICAL INFORMATION
Shelf Life
2 years.

Special Precautions for storage
Do not store above 30°C.
Protect from light and moisture.
Keep out of the reach of children.

To be sold on the prescription of a registered medical practitioner only.

خوراک و ہدایات :
۳۰°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
دوا کو روشنی اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔

صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔

Nature and contents of container / Packaging
KAPDEX (Dexlansoprazole) 30 mg capsules are available in a blister pack of 30's (3x 10's).
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MANUFACTURED BY

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