Remit

DR Capsules*

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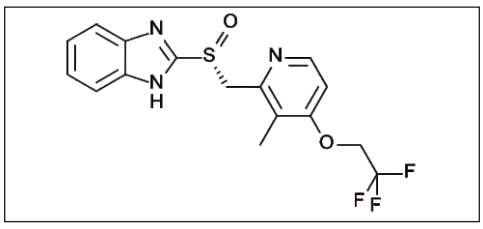
COMPOSITION:
Each capsules contains: Dexlansoprazole Dual Delayed Release Pellets eq. to Dexlansoprazole* .....30 & 60mg

DESCRIPTION:
The active ingredient in Remit (dexlansoprazole) delayed-release capsules, a proton pump inhibitor, is (+)-2-[(R)-{[3-methyl4-(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: C16H14F3N3O2S, with a molecular weight of 369.36. Dexlansoprazole has the following chemical structure:



Remit delayed-release capsules are available in two dosage strengths: 30 mg and 60 mg, per capsule. Each capsule contains enteric-coated granules consisting of dexlansoprazole.

CLINICAL PHARMACOLOGY
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 has been characterized as a gastric proton-pump inhibitor, in that it blocks the final step of acid production.
Pharmacokinetics:
The dual delayed release formulation of Remit capsules results in a dexlansoprazole plasma concentration-time profile with two distinct peaks; the first peak occurs one to two hours after administration, followed by a second peak within four to five hours.Dexlansoprazole is eliminated with a half-life of approximately one to two hours in healthy subjects and in patients with symptomatic GERD. No accumulation of dexlansoprazole occurs after multiple, once daily doses of Remit 30 mg or 60 mg capsules although mean AUCt and Cmax values of dexlansoprazole were slightly higher (less than 10%) on Day 5 than on Day 1.
Absorption
After oral administration of Remit 30 mg or 60 mg capsules to healthy subjects and symptomatic GERD patients, mean Cmax and AUC values of dexlansoprazole increased approximately dose proportionally.
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.
Excretion
Following the administration of Remit capsule, no unchanged dexlansoprazole is excreted in urine.

INDICATIONS AND USAGE
Healing of Erosive Esophagitis
Remit delayed-release capsules are indicated in adults for healing of all grades of erosive esophagitis (EE) for up to eight weeks.
Maintenance of Healed Erosive Esophagitis
Remit capsules are indicated in adults to maintain healing of EE and relief of heartburn for up to six months.
Symptomatic Non-Erosive Gastroesophageal Reflux Disease
Remit capsules are indicated in adults for the treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for four weeks.

CONTRAINDICATIONS
Remit is contraindicated
- In patients with known hypersensitivity to any component of the formulation.
- Hypersensitivity reactions, including anaphylaxis.
- PPIs, including Remit , are contraindicated with rilpivirine-containing products.

ADVERSE REACTIONS
The following serious adverse reactions are described below:
- Acute Interstitial Nephritis
- Cyanocobalamin (Vitamin B-12) Deficiency
- Clostridium difficile Associated Diarrhea
- Bone Fracture
- Hypomagnesemia

DRUG INTERACTIONS

Relevant Interactions Affecting Drugs Co-Administered with Remit and Interactions with Diagnostics

Drug(s)	Recommendation	Comments
Antiretrovirals	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.
Warfarin	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.	Monitor INR and prothrombin time. Dose adjustment of warfarin may be needed to maintain target INR range.
Methotrexate	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.	A temporary withdrawal of Remit may be considered in some patients receiving high-dose methotrexate.
Digoxin	Potential for increased exposure of digoxin.	Monitor digoxin concentrations. Dose adjustment of digoxin may be needed to maintain therapeutic drug concentrations.
Drugs Dependent on Gastric pH for Absorption (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenoloate mofetil, ketoconazole/itraconazole)	Dexlansoprazole can reduce the absorption of other drugs due to its effect on reducing intragastric acidity.	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. Use Remit with caution in transplant patients receiving MMF.
Tacrolimus	Potentially increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.	Monitor tacrolimus whole blood trough concentrations. Dose adjustment of tacrolimus may be needed to maintain therapeutic drug concentrations.

Interactions with Investigations of Neuroendocrine Tumors	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.	Temporarily stop Remit 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	Hyper-response in gastrin secretion in response to secretin stimulation test, falsely suggesting gastrinoma.	Temporarily stop Remit treatment at least 30 days before assessing to allow gastrin levels to return to baseline.
False Positive Urine Tests for THC	False positive urine screening tests for tetrahydrocannabinol (THC) may occur in patients receiving PPIs.	An alternative confirmatory method should be considered to verify positive results.

Clinically Relevant Interactions Affecting Remit When Co-Administered with Other Drugs

Drug(s)	Recommendation	Comments
CYP2C19 or CYP3A4 Inducers	Decreased exposure of dexlansoprazole when used concomitantly with strong inducers	St. John's Wort, rifampin: Avoid concomitant use with Remit
CYP2C19 or CYP3A4 Inhibitors	Increased exposure of dexlansoprazole is expected when used concomitantly with strong inhibitors	Avoid concomitant use with Remit

USE IN SPECIFIC POPULATION

Pregnancy: There are no studies with dexlansoprazole use in pregnant women to inform a drug-associated risk.

***Nursing Mothers*:** There is no information regarding the presence of dexlansoprazole in human milk, the effects on the breastfed infant, or the effects on milk production.

Pediatric Use: Safety and effectiveness of Remit have not been established in pediatric patients. The use of Remit is not recommended for symptomatic non-erosive GERD in pediatric patients less than 1 year of age because studies in this class of drugs have not demonstrated efficacy.

Geriatric Use: No overall differences in safety or effectiveness is observed between these geriatric patients and younger patients and other reported clinical experience has not identified significant differences in responses between geriatric and younger patients, but greater sensitivity of some older individuals cannot be ruled out

Renal Impairment: Renal function should be evaluated in all patients prior to initiation of ribavirin by estimating the patient's creatinine clearance. Patients with CLcr less than or equal to 50 mL/min should receive a reduced dose of ribavirin; and patients with CLcr less than 30 mL/min should receive a reduced dose of peginterferon alfa-2a. The clinical and hematologic status of patients with CLcr less than or equal to 50 mL/min receiving ribavirin should be carefully monitored. Patients with clinically significant laboratory abnormalities or adverse reactions which are persistently severe or worsening should have therapy withdrawn.

Hepatic Impairment: No dosage adjustment for Remit capsules is necessary for patients with mild hepatic impairment (Child-Pugh Class A)

No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C), the use of Remit capsules is not recommended for these patients

WARNINGS AND PRECAUTIONS

Presence of Gastric Malignancy

Symptomatic response with Remit does not preclude the presence of gastric malignancy.

Acute Interstitial Nephritis

Acute interstitial nephritis is observed 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 Remit if acute interstitial nephritis develops.

Cyanocobalamin (Vitamin B-12) Deficiency

Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (Vitamin B-12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy is observed in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed in patients treated with Remit .

Clostridium Difficile Associated Diarrhea

PPI therapy like Remit 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

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.

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, is observed 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), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically

DOSAGE AND ADMINISTRATION

Indication	Recommended Dosage Regimen
Healing of EE	One 60 mg capsule once daily for up to 8 weeks
Maintenance of Healed EE and Relief of Heartburn	One 30 mg capsule once daily*
Symptomatic Non-Erosive GERD	One 30 mg capsule daily for 4 weeks

*Controlled studies did not extend beyond 6 months.

Dosage Adjustment in Adults with Hepatic Impairment for the Healing of EE

For adult patients with moderate hepatic impairment (Child-Pugh Class B), the recommended dosage is 30 mg Remit capsule. The use of Remit capsule is not recommended in patients with severe hepatic impairment (Child-Pugh Class C).

Important Administration Information

Missed doses: 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.

OVERDOSAGE

There have been no reports of significant overdose of Remit . Non-serious adverse reactions observed with twice daily doses of Remit 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.

STORAGE/PRECAUTIONS: Store in a cool, dry and dark place between 15 - 30 °C. Keep all medicines out of the reach of children. To be used on the prescription of Registered Medical Practitioners.

PRESENTATION: Remit Capsules 30mg and 60 mg are available in packing containing 30 capsules .

*Scotmann Specs.

خوراک: ڈاکٹر کی ہدایت کے مطابق۔

احتیاط: روشنی، نمی اور گرمی سے بچائیں۔ 15 سے 30 ڈگری سینٹی گریڈ کے درمیان محفوظ کریں۔ تمام ادویات بچوں کی پہنچ سے دور رکھیں۔ مستند ڈاکٹر کے نسخہ پر فروخت اور استعمال کریں۔

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