Razodex™

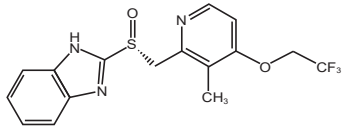
[D e x l a n s o p r a z o l e]

ریزوڈیکس

Capsules 30mg & 60mg

DESCRIPTION

Razodex (Dexlansoprazole), a proton pump inhibitor, is (+)-2-[(R)-{[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl] methyl} sulfinyl]-*1H* benzimidazole. Dexlansoprazole is the *R*-enantiomer of lansoprazole (a racemic mixture of the *R*- and *S*- enantiomers). Its molecular formula is $C_{16}H_{14}F_3N_3O_2S$ and the structural formula is:



Dexlansoprazole

QUALITATIVE & QUANTITATIVE COMPOSITION

Razodex (Dexlansoprazole) is available for oral administration as:

Razodex Capsules 30mg
Each capsule contains:
Enteric-coated pellets of Dexlansoprazole equivalent to Dexlansoprazole... 30mg

Razodex Capsules 60mg
Each capsule contains:
Enteric-coated pellets of Dexlansoprazole equivalent to Dexlansoprazole... 60mg

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. 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 dexlansoprazole 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.

Absorption

After oral administration of dexlansoprazole capsules to healthy subjects and symptomatic GERD patients, mean C_{max} and AUC values of dexlansoprazole increased approximately dose proportionally.

Effect on Food

In healthy subjects receiving dexlansoprazole capsules 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. 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.
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.

Excretion

Following the administration of dexlansoprazole capsule, no unchanged dexlansoprazole is excreted in urine. Apparent clearance (CL/F) in healthy subjects was 11.4 to 11.6 L/hour respectively, after five days of 30mg or 60mg once daily administration.
Dexlansoprazole is eliminated with a half-life of approximately one to two hours in healthy subjects and in patients with symptomatic GERD.

Special Population

Geriatric Population

Dexlansoprazole exhibited higher systemic exposure (AUC) in geriatric subjects (34% higher) than younger patients.

Hepatic Impairment

In patients with moderate hepatic impairment (Child-Pugh Class B) the systemic exposure (AUC) of bound and unbound dexlansoprazole was approximately two times greater compared to subjects with normal hepatic function.

THERAPEUTIC INDICATIONS

Razodex (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.
- To maintain healing of EE and relief of heartburn for up to six months.
- For the treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for four weeks.

DOSAGE AND ADMINISTRATION

Recommended Dosage in Patients 12 Years of Age and Older

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

Special Population

Hepatic Impairment

For adult patients with moderate hepatic impairment (Child-Pugh Class B), the recommended dosage of Razodex (Dexlansoprazole) for the healing of erosive esophagitis is 30mg once daily for up to 8 weeks.

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.

Administration advice:

- For patients that have difficulty swallowing capsules, the contents of a capsule can be sprinkled on applesauce or empty the content of capsule into a clean container with 20mL of water and withdraw the entire mixture into an oral syringe.
- Administer immediately into the mouth. Refill the syringe with 10mL of water, swirl gently and administer.
- Repeat this step one more time.

Administration with water via a nasogastric tube:

- Open the capsule and empty the content of capsule into a clean container with 20mL of water.
- Withdraw the entire mixture into a catheter-tip syringe, swirl the syringe gently in order to keep the granules from settling and immediately inject the mixture through the nasogastric tube into the stomach.
- Do not save the water and granule mixture for later use.
- Refill the syringe with 10mL of water, swirl gently and flush the tube.
- Refill the syringe again with 10mL of water, swirl gently and administer.

CONTRAINDICATIONS

Dexlansoprazole is contraindicated:
- In patients with known hypersensitivity to dexlansoprazole or to any excipient of the product.
- With rilpivirine-containing products.
- In patients with severe hepatic impairment.

ADVERSE REACTIONS

Common

Diarrhea, abdominal pain, nausea, upper respiratory tract infection, vomiting and flatulence.

Less Common

Anemia, lymphadenopathy, angina, arrhythmia, bradycardia, chest pain, edema, myocardial infarction, palpitation, tachycardia, ear pain, tinnitus, vertigo, goiter, eye irritation, eye swelling, abdominal discomfort, abdominal tenderness, abnormal feces, anal discomfort, Barrett's esophagus, bezoar, abnormal bowel sounds, breath odor, colitis microscopic, colonic polyp, constipation, dry mouth, duodenitis, dyspepsia, dysphagia, enteritis, eructation, esophagitis, gastric polyp, gastritis, gastroenteritis, gastrointestinal disorders, gastrointestinal hypermotility disorders, GERD, GI ulcers and perforation, hematemesis, hematochezia, hemorrhoids, impaired gastric emptying, irritable bowel syndrome, mucus stools, oral mucosal blistering, painful defecation, proctitis, paresthesia oral, rectal hemorrhage, retching, asthenia, chest pain, chills, feeling abnormal, inflammation, mucosal inflammation, nodule, pain, pyrexia, biliary colic, cholelithiasis, hepatomegaly, hypersensitivity, candida infections, influenza, nasopharyngitis, oral herpes, pharyngitis, sinusitis, viral infection,

vulvo-vaginal infection, falls, fractures, joint sprains, overdose, procedural pain, sunburn, ALP increased, ALT increased, AST increased, bilirubin decreased/increased, blood creatinine increased, blood gastrin increased, blood glucose increased, blood potassium increased, liver function test abnormal, platelet count decreased, total protein increased, weight increase, appetite changes, hypercalcemia, hypokalemia, arthralgia, arthritis, muscle cramps, musculoskeletal pain, myalgia, altered taste, convulsion, dizziness, headaches, migraine, memory impairment, paresthesia, psychomotor hyperactivity, tremor, trigeminal neuralgia, abnormal dreams, anxiety, depression, insomnia, libido changes, dysuria, micturition urgency, dysmenorrhea, dyspareunia, menorrhagia, menstrual disorder, aspiration, asthma, bronchitis, cough, dyspnea, hiccups, hyperventilation, respiratory tract congestion, sore throat, acne, dermatitis, erythema, pruritus, rash, skin lesion, urticarial, deep vein thrombosis, hot flush, hypertension, anaphylaxis, auditory hallucination, B-cell lymphoma, bursitis, central obesity, acute cholecystitis, dehydration, diabetes mellitus, dysphonia, epistaxis, folliculitis, gout, herpes zoster, hyperlipidemia, hypothyroidism, increased neutrophils, MCHC decrease, neutropenia, rectal tenesmus, restless legs syndrome, somnolence, tonsillitis.

PRECAUTIONS

- Use of proton pump inhibitors (PPIs) may increase risk of Clostridium difficile-associated diarrhea, especially in hospitalized patients. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.
- Increased incidence of osteoporosis-related bone fractures of the hip, spine or wrist may occur with proton pump inhibitor (PPI) therapy. 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.
- Consider obtaining serum magnesium concentrations prior to beginning long-term therapy, especially if taking concomitant digoxin, diuretics or other drugs known to cause hypomagnesemia.
- Acute interstitial nephritis has been observed in patients taking PPIs including dexlansoprazole; may occur at any time during therapy. Discontinue dexlansoprazole, if acute interstitial nephritis develops.
- Prolonged treatment may lead to vitamin B_{12} malabsorption and subsequent vitamin B_{12} deficiency.
- Use of PPIs may increase risk of gastrointestinal infections.
- Symptomatic response with dexlansoprazole does not preclude the presence of gastric malignancy.

DRUG INTERACTIONS

Antiretrovirals
Rilpivirine, atazanavir and nelfinavir when used concomitantly with dexlansoprazole may reduce antiviral effect and promote the development of drug resistance.

Saquinavir
Saquinavir when used concomitantly with dexlansoprazole may increase toxicity of the antiretroviral drugs.

Warfarin
Concomitant use of PPI's with warfarin may increase INR and prothrombin time in patients which may lead to abnormal bleeding and even death.

Methotrexate
Concomitant use of PPIs with methotrexate may elevate and prolong serum concentrations of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities.

Digoxin
Potential for increased exposure of digoxin. Monitor digoxin concentration.

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.

Tacrolimus
Potentially increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.

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.

Interaction with Secretin Stimulation Test
Hyper-response in gastrin secretion in response to secretin stimulation test, falsely suggesting gastrinoma.

False Positive Urine Tests for THC
There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs.

CYP2C19 or CYP3A4 Inducers (St. John's Wort, rifampin)
Decreased exposure of dexlansoprazole when used concomitantly with strong inducers.

CYP2C19 or CYP3A4 Inhibitors (Voriconazole)
Increased exposure of dexlansoprazole is expected when used concomitantly with strong inhibitors.

OVERDOSAGE

Serious adverse events of hypertension have been reported in association with twice daily doses of dexlansoprazole 60mg. Non-serious adverse reactions observed with twice daily doses of dexlansoprazole 60mg 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

Do not store above 30°C.
Protect from sunlight & moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

Razodex (Dexlansoprazole) Capsules 30mg are available in pack of 30's.
Razodex (Dexlansoprazole) Capsules 60mg are available in pack of 30's.

Keep out of reach of children.

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

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
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