

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **DEXLANSOPRAZOLE DELAYED-RELEASE CAPSULES** safely and effectively. See full prescribing information for **DEXLANSOPRAZOLE DELAYED-RELEASE CAPSULES**.

**DEXLANSOPRAZOLE delayed-release capsules, for oral use.**  
Initial U.S. Approval: 1995 (lansoprazole)

### -----RECENT MAJOR CHANGES-----

Dosage and Administration, Dose Adjustment in Patients with Hepatic Impairment for Healing of EE (2.2)	01/2016
Important Administration Information (2.3)	01/2016
Contraindications (4)	01/2016
Warnings and precautions, Cutaneous and Systemic Lupus Erythematosus (5.5)	10/2016
Interaction with Investigations for Neuroendocrine Tumors (5.8)	01/2016

### -----INDICATIONS AND USAGE-----

Dexlansoprazole is a proton pump inhibitor (PPI).  
Dexlansoprazole Delayed-Release Capsules are indicated for:

- Healing of all grades of erosive esophagitis (EE). (1.1)
- Maintenance of healed EE and relief of heartburn. (1.2)
- Treatment of symptomatic non-erosive gastroesophageal reflux disease (GERD). (1.3)

### -----DOSAGE AND ADMINISTRATION-----

Two 30 mg dexlansoprazole delayed-release orally disintegrating tablets are not interchangeable with one 60 mg dexlansoprazole delayed-release capsule. (2.1)

#### Recommended dosage:

- See full prescription information for complete dosing information for Dexlansoprazole Delayed-Release Capsules by indication and dosage adjustment in patients with hepatic impairment. (2.2)

#### Administration Instructions (2.3):

Dexlansoprazole Delayed-Release Capsules

- Take without regard to food.
- Swallow whole; do not chew.
- See full prescribing information for alternative administration options.

### -----DOSAGE FORMS AND STRENGTHS-----

- Delayed-Release Capsules: 60 mg. (3)

### -----CONTRAINDICATIONS-----

- Patients with known hypersensitivity to any component of the formulation. (4)
- Patients receiving rilpivirine-containing products. (4, 7)

### -----WARNINGS AND PRECAUTIONS-----

- Gastric Malignancy: In adults, symptomatic response with dexlansoprazole does not preclude the presence of gastric

malignancy. Consider additional follow-up and diagnostic testing (5.1)

- Acute Interstitial Nephritis: Observed in patients taking PPIs. (5.2)
- Clostridium difficile Associated Diarrhea: PPI therapy may be associated with increased risk. (5.3)
- Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. (5.4)
- Cutaneous and Systemic Lupus Erythematosus: Mostly cutaneous; new onset or exacerbation of existing disease; discontinue dexlansoprazole and refer to specialist for evaluation. (5.5)
- Cyanocobalamin (Vitamin B-12) Deficiency: Daily long-term use (e.g., longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin. (5.6)
- Hypomagnesemia: Reported rarely with prolonged treatment with PPIs. (5.7)
- Interactions with Investigations for Neuroendocrine Tumors: Increases in intragastric pH may result in hypergastrinemia and enterochromaffin-like cell hyperplasia and increased chromogranin A levels which may interfere with diagnostic investigations for neuroendocrine tumors. (5.8, 7)
- Interaction with Methotrexate: Concomitant use with PPIs may elevate and/or prolong serum concentrations of methotrexate and/or its metabolite, possibly leading to toxicity. With high dose methotrexate administration, consider a temporary withdrawal of Dexlansoprazole Delayed-Release Capsules. (5.9,7)

### -----ADVERSE REACTIONS-----

The most common adverse reactions are:

- Adults (≥2%): diarrhea, abdominal pain, nausea, upper respiratory tract infection, vomiting, and flatulence. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

### -----DRUG INTERACTIONS-----

See full prescribing information for a list of clinically important drug interactions (7).

**See 17 for PATIENT COUNSELING INFORMATION and medication guide.**

**Pediatric use information for patients ages 12 to 17 years is approved for Takeda Pharmaceuticals USA, Inc's DEXILANT (dexlansoprazole) delayed-release capsules. However, due to Takeda Pharmaceuticals USA, Inc.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.**

**Issued: 03/2017**

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\*Sections or subsections omitted from the full prescribing information are not listed.

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**FULL PRESCRIBING INFORMATION****1 INDICATIONS AND USAGE****1.1 Healing of Erosive Esophagitis**

Dexlansoprazole Delayed-Release Capsules are indicated for healing of all grades of erosive esophagitis (EE) for up to eight weeks.

**1.2 Maintenance of Healed Erosive Esophagitis and Relief of Heartburn**

Dexlansoprazole Delayed-Release Capsules are indicated to maintain healing of EE and relief of heartburn for up to six months in adults.

**1.3 Treatment of Symptomatic Non-Erosive Gastroesophageal Reflux Disease**

Dexlansoprazole Delayed-Release Capsules are indicated for the treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for four weeks.

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## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosage

Two 30 mg dexlansoprazole delayed-release orally disintegrating tablets are not interchangeable with one 60 mg Dexlansoprazole Delayed-Release Capsule [see *Clinical Pharmacology* (12.3)]

**Table 1: Recommended Dexlansoprazole Delayed-Release Capsules Regimen by Indication**

Indication	Dosage of Dexlansoprazole 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
Symptomatic Non-Erosive GERD	One 30 mg capsule once daily.	4 weeks

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### 2.2 Dosage Adjustment in Patients with Hepatic Impairment for the Healing of EE

For patients with moderate hepatic impairment (Child-Pugh Class B), the recommended dosage is a 30 mg Dexlansoprazole Delayed-Release Capsule once daily for up to 8 weeks. The use of a Dexlansoprazole Delayed-Release Capsule is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) [see *Use in Specific Populations* (8.6)].

### 2.3 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.

#### Dexlansoprazole Delayed-Release Capsules

- Take without regard to food.
- Swallow whole; do not chew.
- For patients who have trouble swallowing capsules, Dexlansoprazole Delayed-Release Capsules can be opened and administered with applesauce as follows:

1. Place one tablespoonful of applesauce into a clean container.
2. Open capsule.
3. Sprinkle intact granules on applesauce.
4. Swallow applesauce and granules immediately. Do not chew granules. Do not save the applesauce and granules for later use.

- Alternatively, the capsule can be administered with water via oral syringe or nasogastric (NG) tube.

#### *Administration with Water in an Oral Syringe*

1. Open the capsule and empty the granules into a clean container with 20 mL of water.
2. Withdraw the entire mixture into a syringe.
3. Gently swirl the syringe in order to keep granules from settling.
4. Administer the mixture immediately into the mouth. Do not save the water and granule mixture for later use.
5. Refill the syringe with 10 mL of water, swirl gently, and administer.
6. Refill the syringe again with 10 mL of water, swirl gently, and administer.

#### *Administration with Water via a NG Tube (≥16 French)*

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

### **3 DOSAGE FORMS AND STRENGTHS**

#### Dexlansoprazole Delayed-Release Capsules

60 mg: strength is an opaque, green capsules with "par" imprinted on the cap and "148" imprinted on the body.

### **4 CONTRAINDICATIONS**

- Dexlansoprazole delayed-release capsules are contraindicated in patients with known hypersensitivity to any component of the formulation [see **Description** (11)]. Hypersensitivity reactions, including anaphylaxis have been reported [see **Adverse Reactions** (6.1, 6.2)]. Acute interstitial nephritis (AIN) has been reported with other proton pump inhibitors (PPIs), including lansoprazole of which Dexlansoprazole is the *R-enantiomer*.
- PPIs, including Dexlansoprazole Delayed-Release Capsules, are contraindicated with rilpivirine-containing products [see **Drug Interactions** (7)]

### **5 WARNINGS AND PRECAUTIONS**

Dexlansoprazole Delayed-Release Capsules, 60 mg contain FD&C Yellow # 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow # 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

#### **5.1 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.

## 5.2 Acute Interstitial Nephritis

Acute interstitial nephritis has been 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 dexlansoprazole if acute interstitial nephritis develops [see **Contraindications** (4)].

## 5.3 *Clostridium difficile*-Associated Diarrhea

Published observational studies suggest that 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 [see **Adverse Reactions** (6.2)].

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

## 5.4 Bone Fracture

Several published observational studies suggest 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 [see **DOSAGE AND ADMINISTRATION** (2) and **ADVERSE REACTIONS** (6.2)].

## 5.5 Cutaneous and Systemic Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported 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 Delayed-Release Capsules, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g., ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

## 5.6 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 have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed in patients treated with dexlansoprazole.

### **5.7 Hypomagnesemia**

Hypomagnesemia, symptomatic and asymptomatic, has been reported 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 [see **Adverse Reactions** (6.2)].

### **5.8 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 [see *Drug Interactions* (7), *Clinical Pharmacology* (12.2)].

### **5.9 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 [see **Drug Interactions** (7)].

## **6 ADVERSE REACTIONS**

The following serious adverse reactions are described below and elsewhere in labeling:

- Acute Interstitial Nephritis [see *Warnings and precautions* (5.2)]
- *Clostridium difficile*-Associated Diarrhea [see *Warnings and Precautions* (5.3)]
- Bone Fracture [see *Warnings and Precautions* (5.4)]
- Cutaneous and Systemic Lupus Erythematosus [see *Warnings and Precautions* (5.5)]
- Cyanocobalamin (Vitamin B-12) Deficiency [see *Warnings and Precautions* (5.6)]
- Hypomagnesemia [see *Warnings and Precautions* (5.7)]

### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults

The safety of dexlansoprazole delayed-release capsules was evaluated in 4548 adult patients in controlled and single-arm clinical trials, including 863 patients treated for at least six months and 203 patients treated for one year. Patients ranged in age from 18 to 90 years (median age 48 years), with 54% female, 85% Caucasian, 8% Black, 4% Asian, and 3% other races. Six randomized controlled clinical trials were conducted for the treatment of EE, maintenance of healed EE, and symptomatic GERD, which included 896 patients on placebo, 455 patients on dexlansoprazole 30 mg capsules, 2218 patients on dexlansoprazole 60 mg capsules, and 1363 patients on lansoprazole 30 mg once daily.

Common Adverse Reactions

The most common adverse reactions ( $\geq 2\%$ ) that occurred at a higher incidence for dexlansoprazole capsules than placebo in the controlled studies are presented in Table 3.

**Table 3: Common Adverse Reactions in Controlled Studies in Adults**

<b>Adverse Reaction</b>	<b>Placebo (N=896) %</b>	<b>Dexlansoprazole 30 mg capsules (N=455) %</b>	<b>Dexlansoprazole 60 mg capsules (N=2218) %</b>	<b>Dexlansoprazole capsules Total (N=2621) %</b>	<b>Lansoprazole 30 mg (N=1363) %</b>
Diarrhea	2.9	5.1	4.7	4.8	3.2
Abdominal Pain	3.5	3.5	4.0	4.0	2.6
Nausea	2.6	3.3	2.8	2.9	1.8
Upper Respiratory Tract Infection	0.8	2.9	1.7	1.9	0.8
Vomiting	0.8	2.2	1.4	1.6	1.1
Flatulence	0.6	2.6	1.4	1.6	1.2

Adverse Reactions Resulting in Discontinuation

In controlled clinical studies, the most common adverse reaction leading to discontinuation from dexlansoprazole capsules was diarrhea (0.7%).

Less Common Adverse Reactions

Other adverse reactions that were reported in controlled studies at an incidence of less than 2% are listed below by body system:

*Blood and Lymphatic System Disorders:* anemia, lymphadenopathy

*Cardiac Disorders:* angina, arrhythmia, bradycardia, chest pain, edema, myocardial infarction, palpitation, tachycardia

*Ear and Labyrinth Disorders:* ear pain, tinnitus, vertigo

*Endocrine Disorders:* goiter

*Eye Disorders:* eye irritation, eye swelling

*Gastrointestinal Disorders:* abdominal discomfort, abdominal tenderness, abnormal feces, anal discomfort, Barrett's esophagus, bezoar, bowel sounds abnormal, 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

*General Disorders and Administration Site Conditions:* adverse drug reaction, asthenia, chest pain, chills, feeling abnormal, inflammation, mucosal inflammation, nodule, pain, pyrexia

*Hepatobiliary Disorders:* biliary colic, cholelithiasis, hepatomegaly

*Immune System Disorders:* hypersensitivity

*Infections and Infestations:* candida infections, influenza, nasopharyngitis, oral herpes, pharyngitis, sinusitis, viral infection, vulvo-vaginal infection

*Injury, Poisoning and Procedural Complications:* falls, fractures, joint sprains, overdose, procedural pain, sunburn

*Laboratory Investigations:* 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

*Metabolism and Nutrition Disorders:* appetite changes, hypercalcemia, hypokalemia

*Musculoskeletal and Connective Tissue Disorders:* arthralgia, arthritis, muscle cramps, musculoskeletal pain, myalgia

*Nervous System Disorders:* altered taste, convulsion, dizziness, headaches, migraine, memory impairment, paresthesia, psychomotor hyperactivity, tremor, trigeminal neuralgia

*Psychiatric Disorders:* abnormal dreams, anxiety, depression, insomnia, libido changes

*Renal and Urinary Disorders:* dysuria, micturition urgency

*Reproductive System and Breast Disorders:* dysmenorrhea, dyspareunia, menorrhagia, menstrual disorder

*Respiratory, Thoracic and Mediastinal Disorders:* aspiration, asthma, bronchitis, cough, dyspnea, hiccups, hyperventilation, respiratory tract congestion, sore throat

*Skin and Subcutaneous Tissue Disorders:* acne, dermatitis, erythema, pruritis, rash, skin lesion, urticaria

*Vascular Disorders:* deep vein thrombosis, hot flush, hypertension

Additional adverse reactions that were reported in a long-term single-arm trial and were considered related to dexlansoprazole by the treating physician included: anaphylaxis, auditory hallucination, B-cell lymphoma, bursitis, central obesity, cholecystitis acute,



dehydration, diabetes mellitus, dysphonia, epistaxis, folliculitis, gout, herpes zoster, hyperlipidemia, hypothyroidism, increased neutrophils, MCHC decrease, neutropenia, rectal tenesmus, restless legs syndrome, somnolence, tonsillitis.

#### Other Adverse Reactions

See the full prescribing information for lansoprazole for other adverse reactions not observed with dexlansoprazole.

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### **6.2 Postmarketing Experience**

The following adverse reactions have been identified during post-approval of dexlansoprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Blood and Lymphatic System Disorders:* autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura

*Ear and Labyrinth Disorders:* deafness

*Eye Disorders:* blurred vision

*Gastrointestinal Disorders:* oral edema, pancreatitis

*General Disorders and Administration Site Conditions:* facial edema

*Hepatobiliary Disorders:* drug-induced hepatitis

*Immune System Disorders:* anaphylactic shock (requiring emergency intervention), exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal)

*Infections and Infestations:* *Clostridium difficile* associated diarrhea

*Metabolism and Nutrition Disorders:* hypomagnesemia, hyponatremia

*Musculoskeletal System Disorders:* bone fracture

*Nervous System Disorders:* cerebrovascular accident, transient ischemic attack

*Renal and Urinary Disorders:* acute renal failure

*Respiratory, Thoracic and Mediastinal Disorders:* pharyngeal edema, throat tightness

*Skin and Subcutaneous Tissue Disorders:* generalized rash, leukocytoclastic vasculitis

## **7 DRUG INTERACTIONS**

Tables 4 and 5 include 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 4: Clinically Relevant Interactions Affecting Drugs Co-Administered with Dexamproprazole and Interactions with Diagnostics**

<b>Antiretrovirals</b>	
<i>Clinical Impact:</i>	<p>The effect of PPIs on antiretroviral drugs is variable. The clinical importance and the mechanisms behind these interactions are not always known.</p> <ul style="list-style-type: none"> <li>• Decreased exposure of some antiretroviral drugs (e.g., rilpivirine, atazanavir, and nelfinavir) when used concomitantly with dexamproprazole may reduce antiviral effect and promote the development of drug resistance.</li> <li>• Increased exposure of other antiretroviral drugs (e.g., saquinavir) when used concomitantly with dexamproprazole may increase toxicity of the antiretroviral drugs.</li> <li>• There are other antiretroviral drugs which do not result in clinically relevant interactions with dexamproprazole.</li> </ul>
<i>Intervention:</i>	<p><u>Rilpivirine-containing products</u>: Concomitant use with dexamproprazole is contraindicated [see <i>Contraindications (4)</i>]. See prescribing information.</p> <p><u>Atazanavir</u>: See prescribing information for atazanavir for dosing information.</p> <p><u>Nelfinavir</u>: Avoid concomitant use with dexamproprazole. See prescribing information for nelfinavir.</p> <p><u>Saquinavir</u>: See the prescribing information for saquinavir and monitor for potential saquinavir toxicities.</p> <p><u>Other antiretrovirals</u>: See prescribing information</p>
<b>Warfarin</b>	
<i>Clinical Impact:</i>	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.
<i>Intervention:</i>	Monitor INR and prothrombin time. Dose adjustment of warfarin may be needed to maintain target INR range. See prescribing information for warfarin.
<b>Methotrexate</b>	
<i>Clinical Impact:</i>	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 [see <i>Warnings and Precautions (5.9)</i> ].
<i>Intervention:</i>	A temporary withdrawal of dexamproprazole may be considered in some patients receiving high-dose methotrexate.
<b>Digoxin</b>	
<i>Clinical Impact:</i>	Potential for increased exposure of digoxin.
<i>Intervention:</i>	Monitor digoxin concentrations. Dose adjustment of digoxin may be needed to maintain therapeutic drug concentrations. See prescribing information for digoxin.
<b>Drugs Dependent on Gastric pH for Absorption (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole/itraconazole)</b>	
<i>Clinical Impact:</i>	Dexamproprazole can reduce the absorption of other drugs due to its effect on reducing intragastric acidity.
<i>Intervention:</i>	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 receiving dexamproprazole and MMF. Use dexamproprazole with caution in transplant patients

	receiving MMF.  See the prescribing information for other drugs dependent on gastric pH for absorption.
<b>Tacrolimus</b>	
<i>Clinical Impact:</i>	Potentially increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.
<i>Intervention:</i>	Monitor tacrolimus whole blood trough concentrations. Dose adjustment of tacrolimus may be needed to maintain therapeutic drug concentrations. See prescribing information for tacrolimus.
<b>Interactions with Investigations of Neuroendocrine Tumors</b>	
<i>Clinical Impact:</i>	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 [see <i>Warnings and Precautions (5.8), Clinical Pharmacology (12.2)</i> ].
<i>Intervention:</i>	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.
<b>Interaction with Secretin Stimulation Test</b>	
<i>Clinical Impact:</i>	Hyper-response in gastrin secretion in response to secretin stimulation test, falsely suggesting gastrinoma.
<i>Intervention:</i>	Temporarily stop dexlansoprazole treatment at least 30 days before assessing to allow gastrin levels to return to baseline [see <i>Clinical Pharmacology (12.2)</i> ].
<b>False Positive Urine Tests for THC</b>	
<i>Clinical Impact:</i>	There has been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs.
<i>Intervention:</i>	An alternative confirmatory method should be considered to verify positive results.

**Table 5: Clinically Relevant Interactions Affecting Dexlansoprazole When Co-Administered with Other Drugs and Substances**

<b>CYP2C19 or CYP3A4 Inducers</b>	
<i>Clinical Impact:</i>	Decreased exposure of dexlansoprazole when used concomitantly with strong inducers [see <i>Clinical Pharmacology (12.3)</i> ].
<i>Intervention:</i>	<u>St. John's Wort, rifampin</u> : Avoid concomitant use with dexlansoprazole <u>Ritonavir-containing products</u> : See prescribing information.
<b>CYP2C19 or CYP3A4 Inhibitors</b>	
<i>Clinical Impact:</i>	Increased exposure of dexlansoprazole is expected when used concomitantly with strong inhibitors [see <i>Clinical Pharmacology (12.3)</i> ].
<i>Intervention:</i>	<u>Voriconazole</u> : See prescribing information

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

There are no studies with dexlansoprazole use in pregnant women to inform a drug-associated risk. In animal reproduction studies, no effects on embryo-fetal development

were observed with the administration of oral dexlansoprazole to rabbits during organogenesis at doses up to 9 times the maximum recommended human dose (MRHD) (based on body surface area) or with administration of oral lansoprazole to rats and rabbits during organogenesis at doses up to 40 and 16 times the MRHD (based on body surface area), respectively [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

## Data

### *Animal Data*

An embryo-fetal development study conducted in rabbits at oral dexlansoprazole doses up to 30 mg/kg/day (approximately nine times the maximum recommended human dexlansoprazole dose [60 mg/day] based on body surface area) during organogenesis showed no effects on fetuses due to dexlansoprazole. In addition, embryo-fetal development studies performed in rats with oral lansoprazole at doses up to 150 mg/kg/day (40 times the recommended human lansoprazole dose based on body surface area) during organogenesis and in rabbits with oral lansoprazole at doses up to 30 mg/kg/day (16 times the recommended human lansoprazole dose based on body surface area) during organogenesis revealed no effects on fetuses due to lansoprazole.

## **8.2 Lactation**

### Risk Summary

There is no information regarding the presence of dexlansoprazole in human milk, the effects on the breastfed infant, or the effects on milk production. However, lansoprazole and its metabolites are present in rat milk [see Data]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for dexlansoprazole and any potential adverse effects on the breastfed child from dexlansoprazole or from the underlying maternal condition.

### Data

When [<sup>14</sup>C] lansoprazole was administered orally at 2 mg/kg to lactating rats 14 days after parturition, milk collected at 0.5, 2 and 6 hours after the lansoprazole dose contained 2- to 6-fold higher concentrations of radioactivity than plasma. Almost all of the radioactivity was determined to be from lansoprazole metabolites.

## **8.4 Pediatric Use**

The safety and effectiveness of dexlansoprazole capsules have not been established in pediatric patients less than 12 years of age.

The use of dexlansoprazole 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.

**Pediatric use information for patients ages 12 to 17 years is approved for Takeda Pharmaceuticals USA, Inc's DEXILANT (dexlansoprazole) delayed-release capsules. However, due to Takeda Pharmaceuticals USA, Inc.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.**

### **8.5 Geriatric Use**

Of the total number of patients (n=4548) in clinical studies of dexlansoprazole, 11% of patients were aged 65 years and over, while 2% were 75 years and over. No overall differences in safety or effectiveness were observed between these 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 [see *Clinical Pharmacology (12.3)*].

### **8.6 Hepatic Impairment**

No dosage adjustment for dexlansoprazole delayed-release capsules is necessary for patients with mild hepatic impairment (Child-Pugh Class A).

In a study of adult patients with moderate hepatic impairment (Child-Pugh Class B) who received a single 60 mg dexlansoprazole delayed-release capsule, there was a significant increase in systemic exposure of dexlansoprazole compared to healthy subjects with normal hepatic function [see *Clinical Pharmacology (12.3)*]. Therefore, for patients with moderate hepatic impairment (Child-Pugh Class B), dosage reduction is recommended for the healing of EE [see *Dosage and Administration (2.2)*].

No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C); the use of dexlansoprazole delayed-release capsules is not recommended for these patients [see *Dosage and Administration (2.2)*].

## **10 OVERDOSAGE**

There have been no reports of significant overdose with dexlansoprazole. Multiple doses of dexlansoprazole 120 mg and a single dose of dexlansoprazole 300 mg did not result in death or other severe adverse events. However, serious adverse events of hypertension have been reported 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.

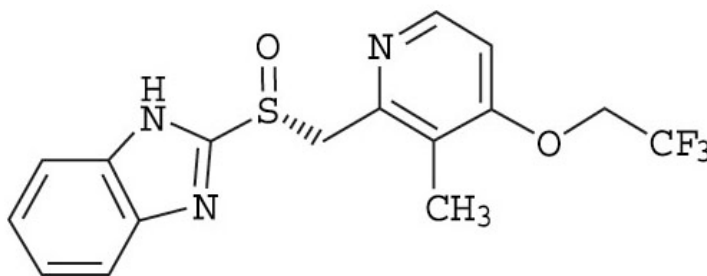
In the event of over-exposure, treatment should be symptomatic and supportive.

If over-exposure occurs, call your poison control center at 1-800-222-1222 for current information on the management of poisoning or over-exposure.

## **11 DESCRIPTION**

The active ingredient in Dexlansoprazole Delayed-Release Capsules, a proton pump inhibitor, 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:



Dexlansoprazole is a white to nearly white crystalline powder which melts with decomposition at 140°C. Dexlansoprazole is freely soluble in dimethylformamide, methanol, dichloromethane, ethanol, and ethyl acetate; and soluble in acetonitrile; slightly soluble in ether; and very slightly soluble in water; and practically insoluble in hexane.

Dexlansoprazole is stable when exposed to light. Dexlansoprazole is more stable in neutral and alkaline conditions than acidic conditions.

Dexlansoprazole is supplied for oral administration as a dual delayed-release formulation in capsules. The capsules contain dexlansoprazole in a mixture of two types of enteric-coated granules with different pH-dependent dissolution profiles [see **Clinical Pharmacology** (12.3)].

Dexlansoprazole delayed-release capsules are available in one dosage strength: 60 mg per capsule. Each capsule contains enteric-coated granules consisting of dexlansoprazole (active ingredient) and the following inactive ingredients: sugar spheres, calcium hydroxide, colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, mannitol, methacrylic acid copolymer, polyethylene glycol, polysorbate 80, triethyl citrate, sodium lauryl sulfate and talc. The capsule shell is made of hypromellose, titanium dioxide, and colorants FD&C Blue #1, FD&C Yellow #5\*, and FD&C Yellow #6. The black imprinting ink contains: shellac glaze in ethanol, iron oxide black, N-butyl alcohol, isopropyl alcohol, propylene glycol and ammonium hydroxide.

\*Contains FD&C Yellow No. 5 (tartrazine) [see **Warnings and Precautions** (5)].

## 12 CLINICAL PHARMACOLOGY

### 12.1 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<sup>+</sup>, K<sup>+</sup>)-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.

## 12.2 Pharmacodynamics

### Antisecretory Activity

The effects of dexlansoprazole 60 mg capsules (n=20) or lansoprazole 30 mg (n=23) once daily for five days on 24 hour intragastric pH were assessed in healthy subjects in a multiple-dose crossover study. The results are summarized in Table 6.

Table 6: Effect on 24 Hour Intragastric pH on Day 5 After Administration of Dexlansoprazole or Lansoprazole	
Dexlansoprazole 60 mg capsules	Lansoprazole 30 mg
Mean Intragastric pH	
4.55	4.13
% Time Intragastric pH > 4 (hours)	
71 (17 hours)	60 (14 hours)

### Serum Gastrin Effects

The effect of dexlansoprazole on serum gastrin concentrations was evaluated in approximately 3460 patients in clinical trials up to eight weeks and in 1023 patients for up to six to 12 months. The mean fasting gastrin concentrations increased from baseline during treatment with dexlansoprazole 30 mg and 60 mg capsules. In patients treated for more than six months, mean serum gastrin levels increased during approximately the first three months of treatment and were stable for the remainder of treatment. Mean serum gastrin levels returned to pre-treatment levels within one month of discontinuation of treatment.

Increased gastrin causes enterochromaffin-like cell hyperplasia and increased serum CgA levels. The increased CgA levels may cause false positive results in diagnostic investigations for neuroendocrine tumors [see **Warnings and Precautions** (5.8)].

### Enterochromaffin-Like Cell (ECL) Effects

There were no reports of ECL cell hyperplasia in gastric biopsy specimens obtained from 653 patients treated with dexlansoprazole 30 mg, 60 mg or 90 mg capsules for up to 12 months.

During lifetime exposure of rats dosed daily with up to 150 mg/kg/day of lansoprazole, marked hypergastrinemia was observed followed by ECL cell proliferation and formation of carcinoid tumors, especially in female rats [see **Nonclinical Toxicology** (13.1)].

### Cardiac Electrophysiology

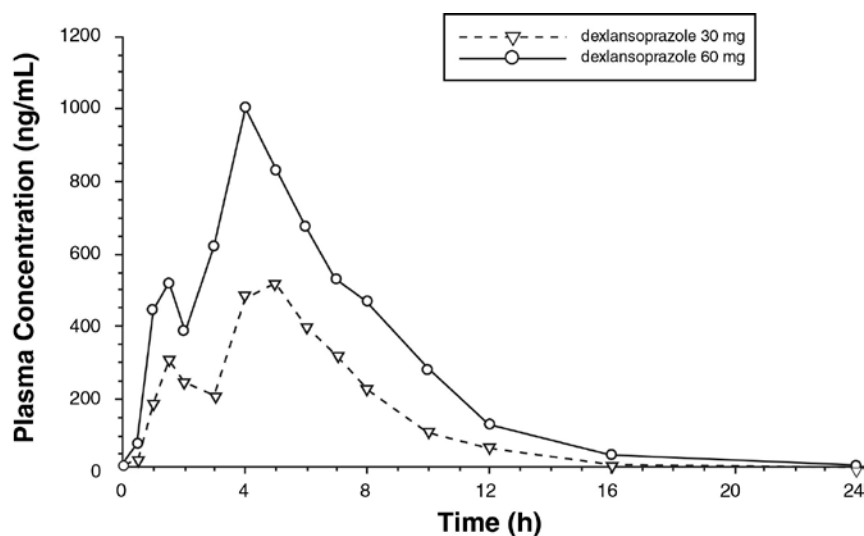
At a dose five times the maximum recommended dose, dexlansoprazole does not prolong the QT interval to any clinically relevant extent.

## 12.3 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 (see *Figure 1*). 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 dexlansoprazole 30 mg or 60 mg capsules although mean  $AUC_t$  and  $C_{max}$  values of dexlansoprazole were slightly higher (less than 10%) on Day 5 than on Day 1.

**Figure 1: Mean Plasma Dexlansoprazole Concentration - Time Profile Following Oral Administration of 30 mg or 60 mg Dexlansoprazole Delayed-Release Capsules Once Daily for 5 Days in Healthy Adult Subjects**



The pharmacokinetics of dexlansoprazole are highly variable, with percent coefficient of variation (CV%) values for  $C_{max}$ ,  $AUC$ , and  $CL/F$  of greater than 30% (see *Table 7*).

Dose (mg)	$C_{max}$ (ng/mL)	$AUC_{24}$ (ng·h/mL)	$CL/F$ (L/h)
30	658 (40%) (N=44)	3275 (47%) (N=43)	11.4 (48%) (N=43)
60	1397 (51%) (N=79)	6529 (60%) (N=73)	11.6 (46%) (N=41)

### Absorption

After oral administration of dexlansoprazole 30 mg or 60 mg capsules to healthy subjects and symptomatic GERD patients, mean  $C_{max}$  and  $AUC$  values of dexlansoprazole increased approximately dose proportionally (see *Figure 1*).

When granules of dexlansoprazole 60 mg capsules 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 [see **Dosage and Administration** (2.3)].



Two 30 mg dexlansoprazole delayed-release orally disintegrating tablets are not interchangeable with one 60 mg dexlansoprazole delayed-release capsule because systemic exposure is lower [see **Dosage and Administration** (2.1)].

#### Effect on Food

In food-effect studies 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) [see *Dosage and Administration* (2.3)].

#### 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 ( $V_z/F$ ) after multiple doses in symptomatic GERD patients was 40 L.

#### Elimination

##### *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.

##### *Excretion*

Following the administration of dexlansoprazole delayed-release capsules, no unchanged dexlansoprazole is excreted in urine. Following the administration of [ $^{14}$ C] 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/h, respectively, after five days of 30 or 60 mg once daily administration.

#### **Special Populations**

##### *Age: Pediatric Population*

The pharmacokinetics of dexlansoprazole in patients under the age of 12 years have not been studied.

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### Age: Geriatric Population

The terminal elimination half-life of dexlansoprazole is significantly increased in geriatric subjects compared to younger subjects (2.2 and 1.5 hours, respectively). Dexlansoprazole exhibited higher systemic exposure (AUC) in geriatric subjects (34% higher) than younger subjects. [see **Use in Specific Populations** (8.5)].

### Sex

In a study of 12 male and 12 female healthy subjects who received a single oral dose of dexlansoprazole 60 mg capsules, females had higher systemic exposure (AUC) (43% higher) than males. This difference in exposure between males and female does not represent a significant safety concern.

### Renal Impairment

Dexlansoprazole is extensively metabolized in the liver to inactive metabolites, and no parent drug is recovered in the urine following an oral dose of dexlansoprazole. Therefore, the pharmacokinetics of dexlansoprazole are not expected to be altered in patients with renal impairment, and no studies were conducted in patients with renal impairment. In addition, the pharmacokinetics of lansoprazole were not clinically different in patients with mild, moderate or severe renal impairment compared to healthy subjects with normal renal function.

### Hepatic Impairment

In a study of 12 patients with moderate hepatic impairment (Child-Pugh Class B) who received a single oral dose of 60 mg dexlansoprazole capsules, the systemic exposure (AUC) of bound and unbound dexlansoprazole was approximately two times greater compared to subjects with normal hepatic function. This difference in exposure was not due to a difference in protein binding. No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C) [see **Dosage and Administration** (2.2), **Use in Specific Populations** (8.6)].

## **Drug-Drug Interactions**

Effect of Dexlansoprazole on other drugs

### Cytochrome P 450 Interactions

Dexlansoprazole is metabolized, in part, by CYP2C19 and CYP3A4 [see **Clinical Pharmacology** (12.3)].

*In vitro* studies have shown that dexlansoprazole is not likely to inhibit CYP isoforms 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1 or 3A4. As such, no clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Furthermore, *in vivo* studies showed that dexlansoprazole did not have an impact on the pharmacokinetics of coadministered phenytoin (CYP2C9 substrate) or theophylline (CYP1A2 substrate). The subjects' CYP1A2 genotypes in the drug-drug interaction study with theophylline were not determined. Although *in vitro* studies indicated that dexlansoprazole has the potential to inhibit CYP2C19 *in vivo*, an *in vivo* drug-drug interaction study in mainly CYP2C19 extensive and intermediate metabolizers has shown that dexlansoprazole does not affect the pharmacokinetics of diazepam (CYP2C19 substrate).

### Clopidogrel

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. A study of healthy subjects who were CYP2C19 extensive metabolizers, receiving once daily administration of clopidogrel 75 mg alone or concomitantly with dexlansoprazole 60 mg capsules (n=40), for nine days was conducted. The mean AUC of the active metabolite of clopidogrel was reduced by approximately 9% (mean AUC ratio was 91%, with 90% CI of 86 to 97%) when dexlansoprazole was coadministered compared to administration of clopidogrel alone. Pharmacodynamic parameters were also measured and demonstrated that the change in inhibition of platelet aggregation (induced by 5 mcM ADP) was related to the change in the exposure to clopidogrel active metabolite. The effect of exposure to the active metabolite of clopidogrel and on clopidogrel-induced platelet inhibition is not considered clinically important.

#### *Effect of Other Drugs on Dexlansoprazole*

Because dexlansoprazole is metabolized by CYP2C19 and CYP3A4, inducers and inhibitors of these enzymes may potentially alter exposure of dexlansoprazole.

### **12.5 Pharmacogenomics**

#### Effect of CYP2C19 Polymorphism on Systemic Exposure of Dexlansoprazole

Systemic exposure of dexlansoprazole is generally higher in intermediate and poor metabolizers. In male Japanese subjects who received a single dose of dexlansoprazole 30 mg or 60 mg capsules (N=2 to 6 subjects/group), mean dexlansoprazole C<sub>max</sub> and AUC values were up to two times higher in intermediate compared to extensive metabolizers; in poor metabolizers, mean C<sub>max</sub> was up to four times higher and mean AUC was up to 12 times higher compared to extensive metabolizers. Though such study was not conducted in Caucasians and African Americans, it is expected dexlansoprazole exposure in these races will be affected by CYP2C19 phenotypes as well.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

The carcinogenic potential of dexlansoprazole was assessed using lansoprazole studies. In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with lansoprazole at doses of 5 to 150 mg/kg/day, about 1 to 40 times the exposure on a body surface (mg/m<sup>2</sup>) basis of a 50 kg person of average height [1.46 m<sup>2</sup> body surface area (BSA)] given the recommended human dose of lansoprazole 30 mg/day.

Lansoprazole produced dose-related gastric ECL cell hyperplasia and ECL cell carcinoids in both male and female rats [see **Clinical Pharmacology** (12.2)].

In rats, lansoprazole also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg/kg/day (4 to 40 times the recommended human lansoprazole dose based on BSA) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat.

In a 24 month carcinogenicity study, CD-1 mice were treated orally with lansoprazole doses of 15 to 600 mg/kg/day, 2 to 80 times the recommended human lansoprazole dose based on BSA. Lansoprazole produced a dose-related increased incidence of gastric ECL cell

hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg lansoprazole/kg/day (40 to 80 times the recommended human lansoprazole dose based on BSA) and female mice treated with 150 to 600 mg lansoprazole/kg/day (20 to 80 times the recommended human lansoprazole dose based on BSA) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg/kg/day (10 to 80 times the recommended human lansoprazole dose based on BSA).

A 26 week p53 (+/-) transgenic mouse carcinogenicity study of lansoprazole was not positive.

Lansoprazole was positive in the Ames test and the *in vitro* human lymphocyte chromosomal aberration assay. Lansoprazole was not genotoxic in the *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) test, the *in vivo* mouse micronucleus test or the rat bone marrow cell chromosomal aberration test.

Dexlansoprazole was positive in the Ames test and in the *in vitro* chromosome aberration test using Chinese hamster lung cells. Dexlansoprazole was negative in the *in vivo* mouse micronucleus test.

The potential effects of dexlansoprazole on fertility and reproductive performance were assessed using lansoprazole studies. Lansoprazole at oral doses up to 150 mg/kg/day (40 times the recommended human lansoprazole dose based on BSA) was found to have no effect on fertility and reproductive performance of male and female rats.

## 14 CLINICAL STUDIES

### 14.1 Healing of Erosive Esophagitis in Adults

Two multi-center, double-blind, active-controlled, randomized, eight week studies were conducted in patients with endoscopically confirmed EE. Severity of the disease was classified based on the Los Angeles Classification Grading System (Grades A to D). Patients were randomized to one of the following three treatment groups: Dexlansoprazole 60 mg capsules daily, dexlansoprazole 90 mg capsules daily or lansoprazole 30 mg daily. Patients who were *H. pylori* positive or who had Barrett's Esophagus and/or definite dysplastic changes at baseline were excluded from these studies. A total of 4092 patients were enrolled and ranged in age from 18 to 90 years (median age 48 years) with 54% male. Race was distributed as follows: 87% Caucasian, 5% Black and 8% other. Based on the Los Angeles Classification, 71% of patients had mild EE (Grades A and B) and 29% of patients had moderate to severe EE (Grades C and D) before treatment.

The studies were designed to test non-inferiority. If non-inferiority was demonstrated then superiority would be tested. Although non-inferiority was demonstrated in both studies, the finding of superiority in one study was not replicated in the other.

The proportion of patients with healed EE at Week 4 or 8 is presented below in Table 9.

**Table 9: EE Healing Rates\* in Adults: All Grades**

Study	Number of Patients (N) †	Treatment Group (daily)	Week 4 % Healed	Week 8 ‡ % Healed	(95% CI) for the Treatment Difference (Dexlansoprazole–Lansoprazole) by Week 8
1	657	Dexlansoprazole 60 mg capsules	70	87	(-1.5, 6.1) §
	648	Lansoprazole 30 mg	65	85	
2	639	Dexlansoprazole 60 mg capsules	66	85	(2.2, 10.5) §
	656	Lansoprazole 30 mg	65	79	

CI = Confidence interval

\* Based on crude rate estimates, patients who did not have endoscopically documented healed EE and prematurely discontinued were considered not healed.

† Patients with at least one post baseline endoscopy

‡ Primary efficacy endpoint

§ Demonstrated non-inferiority to lansoprazole

Dexlansoprazole 90 mg capsules were studied and did not provide additional clinical benefit over dexlansoprazole 60 mg.

#### 14.2 Maintenance of Healed Erosive Esophagitis and Relief of Heartburn in Adults

A multi-center, double-blind, placebo-controlled, randomized study was conducted in patients who successfully completed an EE study and showed endoscopically confirmed healed EE. Maintenance of healing and symptom resolution over a six month period were evaluated with dexlansoprazole 30 mg or 60 mg capsules once daily compared to placebo. A total of 445 patients were enrolled and ranged in age from 18 to 85 years (median age 49 years), with 52% female. Race was distributed as follows: 90% Caucasian, 5% Black and 5% other.

Sixty-six percent of patients treated with 30 mg of dexlansoprazole capsules remained healed over the six-month time period as confirmed by endoscopy (see *Table 10*).

**Table 10: Maintenance Rates\* of Healed EE at Month 6 in Adults**

Number of Patients (N) †	Treatment Group (daily)	Maintenance Rate (%)
125	Dexlansoprazole 30 mg capsules	66.4‡
119	Placebo	14.3

\* Based on crude rate estimates, patients who did not have endoscopically documented relapse and prematurely discontinued were considered to have relapsed.

† Patients with at least one post baseline endoscopy

‡ Statistically significant vs placebo

Dexlansoprazole 60 mg capsules were studied and did not provide additional clinical benefit over dexlansoprazole 30 mg capsules daily.

The effect of dexlansoprazole 30 mg capsules on maintenance of relief of heartburn was also evaluated. Upon entry into the maintenance study, a majority of patients' baseline heartburn severity was rated as none. Dexlansoprazole 30 mg capsules demonstrated a statistically significantly higher percent of 24 hour heartburn-free periods compared to placebo over the six month treatment period (see *Table 11*). The majority of patients treated with placebo discontinued due to relapse of EE between month two and month six.

**Table 11: Median Percentage of 24Hour Heartburn-Free Periods of the Maintenance of Healed EE Study in Adults**

Treatment Group (daily)	Overall Treatment*		Month 1		Month 6	
	N	Heartburn-Free 24-hour Periods (%)	N	Heartburn-Free 24-hour Periods (%)	N	Heartburn-Free 24-hour Periods (%)
Dexlansoprazole 30 mg capsules	132	96.1 <sup>†</sup>	126	96.7	80	98.3
Placebo	141	28.6	117	28.6	23	73.3

\*Secondary efficacy endpoint

<sup>†</sup> Statistically significant vs placebo

### 14.3 Treatment of Symptomatic Non-Erosive GERD in Adults

A multi-center, double-blind, placebo-controlled, randomized, four week study was conducted in patients with a diagnosis of symptomatic non-erosive GERD made primarily by presentation of symptoms. These patients who identified heartburn as their primary symptom, had a history of heartburn for six months or longer, had heartburn on at least four of seven days immediately prior to randomization and had no esophageal erosions as confirmed by endoscopy. However, patients with symptoms which were not acid-related may not have been excluded using these inclusion criteria. Patients were randomized to one of the following treatment groups: Dexlansoprazole 30 mg daily, 60 mg daily, or placebo. A total of 947 patients were enrolled and ranged in age from 18 to 86 years (median age 48 years) with 71% female. Race was distributed as follows: 82% Caucasian, 14% Black and 4% other.

Dexlansoprazole 30 mg capsules provided statistically significantly greater percent of days with heartburn-free 24 hour periods over placebo as assessed by daily diary over four weeks (see *Table 12*). Dexlansoprazole 60 mg capsules was studied and provided no additional clinical benefit over dexlansoprazole 30 mg capsules.

**Table 12: Median Percentages of 24 Hour Heartburn-Free Periods During the 4 Week Treatment Period of the Symptomatic Non-Erosive GERD Study in Adults**

N	Treatment Group (daily)	Heartburn-Free 24-hour Periods (%)
312	Dexlansoprazole 30 mg capsules	54.9*
310	Placebo	18.5

\*Statistically significant vs placebo

A higher percentage of patients on dexlansoprazole 30 mg capsules had heartburn-free 24 hour periods compared to placebo as early as the first three days of treatment and this was

sustained throughout the treatment period (percentage of patients on Day 3: dexlansoprazole 38% versus placebo 15%; on Day 28: dexlansoprazole 63% versus placebo 40%).

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## **16 HOW SUPPLIED/STORAGE AND HANDLING**

Dexlansoprazole Delayed-Release Capsules, 60 mg, are opaque, green with "par" imprinted on the cap and "148" imprinted on the body.

<u>NDC Number</u>	<u>Size</u>
49884-148-11	Bottle of 30
49884-148-10	Bottle of 1000

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

## **17 PATIENT COUNSELING INFORMATION**

Advise the patients to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

### Adverse Reactions

Advise patients to report to their healthcare provider if they experience any signs or symptoms consistent with:

- Hypersensitivity Reactions [see *Contraindications (4)*].
- Acute Interstitial Nephritis [see *Warnings and Precautions (5.2)*].
- *Clostridium difficile*-Associated Diarrhea [see *Warnings and Precautions (5.3)*].
- Bone Fracture [see *Warnings and Precautions (5.4)*].
- Cutaneous and Systemic Lupus Erythematosus [see *Warnings and Precautions (5.5)*].
- Cyanocobalamin (Vitamin B-12) Deficiency [see *Warnings and Precautions (5.6)*].
- Hypomagnesemia [see *Warnings and Precautions (5.7)*].

### Drug Interactions

Advise patients to report to their healthcare provider if they are taking high-dose methotrexate [see *Warnings and Precautions (5.9)*].

### Administration

- 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.

*Dexlansoprazole Delayed-Release Capsules*

- Take without regard to food.
- Swallow whole; do not chew
- Can be opened and sprinkled on applesauce for patients who have trouble swallowing the capsule.
- Alternatively, the capsule can be administered with water via oral syringe or NG tube, as described in the Instructions for Use.



## MEDICATION GUIDE

### Dexlansoprazole (DEX lan SOE pra zol) Delayed-Release Capsules

Read this Medication Guide before you start taking Dexlansoprazole Delayed-Release Capsules and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

Dexlansoprazole Delayed-Release Capsules, 60 mg contain FD&C Yellow # 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow # 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

**What is the most important information that I should know about dexlansoprazole delayed-release capsules?**

**Dexlansoprazole may help your acid-related symptoms, but you could still have serious stomach problems. Talk with your doctor.**

**Dexlansoprazole can cause serious side effects, including:**

- **A type of kidney problem (acute interstitial nephritis).** Some people who take proton pump inhibitor (PPI) medicines, including Dexlansoprazole Delayed-Release Capsules, may develop a kidney problem called acute interstitial nephritis, that can happen at any time during treatment with PPI medicines. Call your doctor right away if you have a decrease in the amount that you urinate or if you have blood in your urine.
- **Diarrhea.** Dexlansoprazole may increase your risk of getting severe diarrhea. This diarrhea may be caused by an infection (*Clostridium difficile*) in your intestines.

Call your doctor right away if you have watery stool, stomach pain, and fever that does not go away.

- **Bone fractures.** People who take multiple daily doses of PPI medicines for a long period of time (a year or longer) may have an increased risk of fractures of the hip, wrist or spine. You should take dexlansoprazole exactly as prescribed, at the lowest dose possible for your treatment and for the shortest time needed. Talk to your doctor about your risk of bone fracture if you take dexlansoprazole.
- **Certain types of lupus erythematosus.** Lupus erythematosus is an autoimmune disorder (the body's immune cells attack other cells or organs in the body). Some people who take PPI medicines may develop certain types of lupus erythematosus or have worsening of the lupus they already have. Call your doctor right away if you have new or worsening joint pain or a rash on your cheeks or arms that gets worse in the sun.

Dexlansoprazole can have other serious side effects. See **“What are the possible side effects of dexlansoprazole?”**

**What is dexlansoprazole?**

Dexlansoprazole is a prescription medicine called a proton pump inhibitor (PPI).  
Dexlansoprazole reduces the amount of acid in your stomach.

**Dexlansoprazole delayed-release capsules are used:**

- for up to 8 weeks to heal acid-related damage to the lining of the esophagus (called erosive esophagitis or EE).
- for up to 6 months in adults to continue healing of erosive esophagitis and relief of heartburn.
- for 4 weeks to treat heartburn related to gastroesophageal reflux disease (GERD).

GERD happens when acid from your stomach enters the tube (esophagus) that connects your mouth to your stomach. This may cause a burning feeling in your chest or throat, sour taste or burping.

It is not known if dexlansoprazole is safe and effective in children under 12 years of age.  
Dexlansoprazole is not effective for symptoms of GERD in children under 1 year of age.

**Who should not take dexlansoprazole?**

**Do not take dexlansoprazole delayed-release capsules if you:**

- are allergic to dexlansoprazole or any of the other ingredients in dexlansoprazole delayed-release capsules. See the end of this Medication Guide for a complete list of ingredients in dexlansoprazole delayed-release capsules.
- are taking a medicine that contains rilpivirine (EDURANT, COMPLERA) used to treat HIV-1 (Human Immuno-deficiency Virus)

**What should I tell my doctor before taking dexlansoprazole?**

**Before you take dexlansoprazole, tell your doctor if you:**

- have been told that you have low magnesium levels in your blood
- have liver problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if dexlansoprazole will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if dexlansoprazole passes into your breast milk or if it will affect your baby or your breast milk. Talk to your doctor about the best way to feed your baby if you take dexlansoprazole.

**Tell your doctor about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Dexlansoprazole may affect how other medicines work, and other medicines may affect how dexlansoprazole works.

Especially tell your doctor if you take methotrexate (Otrexup, Rasuvo, Trexall)  
Know the medicines that you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

**How should I take dexlansoprazole delayed-release capsules?**

- Take dexlansoprazole delayed-release capsules exactly as prescribed by your doctor.

- Do not change your dose or stop taking dexlansoprazole delayed-release capsules without talking to your doctor first.
- Take dexlansoprazole delayed-release capsules with or without food.
- Swallow dexlansoprazole delayed-release capsules whole. Do not chew dexlansoprazole delayed-release capsules or the granules that are in the capsules.
- If you have trouble swallowing a whole capsule, you can open the capsule and take the contents in applesauce. See the “Instructions for Use” at the end of this Medication Guide for instructions on how to take dexlansoprazole delayed-release capsules with applesauce.
- See the “Instructions for Use” at the end of this Medication Guide for instructions on how to mix and give dexlansoprazole delayed-release capsules with water using an oral syringe or through a nasogastric tube.
- If you miss a dose of dexlansoprazole delayed-release capsules, take it as soon as you remember. If it is almost time for your next dose, do not take the missed dose. Take the next dose at your regular time. Do not take 2 doses at the same time to make up for the missed dose.
- If you take too much dexlansoprazole delayed-release capsules, call your doctor or your poison control center at 1-800-222-1222 right away or go to the nearest hospital emergency room.

### **What are the possible side effects of dexlansoprazole?**

#### **Dexlansoprazole may cause serious side effects, including:**

- **See “What is the most important information I should know about dexlansoprazole?”**
- **Vitamin B-12 deficiency.** Dexlansoprazole reduces the amount of acid in your stomach. Stomach acid is needed to absorb Vitamin B-12 properly. Talk with your doctor about the possibility of Vitamin B-12 deficiency if you have been on dexlansoprazole for a long time (more than 3 years).
- **Low magnesium levels in your body.** This problem can be serious. Low magnesium can happen in some people who take a proton pump inhibitor medicine for at least 3 months. If low magnesium levels happen, it is usually after a year of treatment. You may or may not have symptoms of low magnesium.

Tell your doctor right away if you develop any of these symptoms:

- seizures
- dizziness
- abnormal or fast heartbeat
- jitteriness
- jerking movements or shaking (tremors)
- muscle weakness
- spasms of the hands and feet
- cramps or muscle aches
- spasm of the voice box

Your doctor may check the level of magnesium in your body before you start taking dexlansoprazole, or during treatment, if you will be taking dexlansoprazole for a long period of time.

**The most common side effects of dexlansoprazole in adults include:**

- diarrhea
- stomach pain
- nausea
- common cold
- vomiting
- gas

Other side effects:

**Serious allergic reactions.** Tell your doctor if you get any of the following symptoms with dexlansoprazole:

- rash
- face swelling
- throat tightness
- difficulty breathing

Your doctor may stop dexlansoprazole if these symptoms happen.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of dexlansoprazole. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store dexlansoprazole delayed-release capsules?**

- Store dexlansoprazole delayed-release capsules at room temperature between 68° and 77°F (20° to 25°C).

**Keep dexlansoprazole and all medicines out of the reach of children.**

**General information about the safe and effective use of dexlansoprazole**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use dexlansoprazole for a condition for which it was not prescribed. Do not give dexlansoprazole to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about dexlansoprazole. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about dexlansoprazole that is written for healthcare professionals.

For more information, go to [www.pparpharm.com](http://www.pparpharm.com) or call 1-800-828-9393.

## **What are the ingredients in dexlansoprazole delayed-release capsules?**

Active ingredient: dexlansoprazole.

Inactive ingredients: sugar spheres, calcium hydroxide, colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, mannitol, methacrylic acid copolymer, polyethylene glycol, polysorbate 80, triethyl citrate, sodium lauryl sulfate and talc. The capsule shell is made of hypromellose, titanium dioxide, and colorants FD&C Blue #1, FD&C Yellow #5, and FD&C Yellow #6. The black imprinting ink contains: shellac glaze in ethanol, iron oxide black, N-butyl alcohol, isopropyl alcohol, propylene glycol and ammonium hydroxide.

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### **Instructions for Use Dexlansoprazole (DEX lan SOE pra zol) Delayed-Release Capsules**

#### **Taking dexlansoprazole delayed-release capsules with applesauce:**

1. Place 1 tablespoon of applesauce into a clean container.
2. Carefully open the capsule and sprinkle the granules onto the applesauce.
3. Swallow the applesauce and granules right away. Do not chew the granules. Do not save the applesauce and granules for later use.

#### **Giving dexlansoprazole delayed-release capsules with water using an oral syringe:**

1. Place 20 mL of water into a clean container.
2. Carefully open the capsule and empty the granules into the container of water.
3. Use an oral syringe to draw up the water and granule mixture.
4. Gently swirl the oral syringe to keep the granules from settling.
5. Place the tip of the oral syringe in your mouth. Give the medicine right away. Do not save the water and granule mixture for later use.
6. Refill the syringe with 10 mL of water and swirl gently. Place the tip of the oral syringe in your mouth and give the medicine that is left in the syringe.
7. Repeat step 6.

#### **Giving dexlansoprazole delayed-release capsules with water through a nasogastric tube (NG tube):**

For people who have an NG tube that is **size 16 French or larger**, dexlansoprazole delayed-release capsules may be given as follows:

1. Place 20 mL of water into a clean container.
2. Carefully open the capsule and empty the granules into the container of water.
3. Use a 60 mL catheter-tip syringe to draw up the water and granule mixture.
4. Gently swirl the catheter-tip syringe to keep the granules from settling.
5. Connect the catheter-tip syringe to the NG tube.
6. Give the mixture right away through the NG tube into the stomach. Do not save the water and granule mixture for later use.

7. Refill the catheter-tip syringe with 10 mL of water and swirl gently. Flush the NG tube with the water.
8. Repeat step 7.

**How should I store dexlansoprazole delayed-release capsules?**

- Store dexlansoprazole delayed-release capsules at room temperature between 68° and 77°F (20° to 25°C).

**Keep dexlansoprazole delayed-release capsules and all medicines out of reach of children.**

This Medication Guide and Instructions for Use have been approved by the U.S. Food and Drug Administration.

**Manufactured For:**

**Par Pharmaceutical**

**Chestnut Ridge, NY 10977**

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