

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DEXILANT safely and effectively. See full prescribing information for DEXILANT.

DEXILANT (dexlansoprazole) delayed-release capsules, for oral use

DEXILANT SoluTab (dexlansoprazole) delayed-release orally disintegrating tablets, for oral use

Initial U.S. Approval: 1995 (lansoprazole)

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

Indications and Usage (1)	01/2016
Dosage and Administration, Recommended Dose (2.1)	01/2016
Dose Adjustment in Adults with Hepatic Impairment for Healing of EE (2.2)	01/2016
Dosage and Administration, Important Administration Information (2.3)	01/2016
Contraindications (4)	01/2016
Warnings and Precautions, Interaction with Diagnostic Investigations for Neuroendocrine Tumors. (5.7)	01/2016

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

DEXILANT is a proton pump inhibitor (PPI).

DEXILANT delayed-release capsules (DEXILANT capsules) are indicated in adults for:

- Healing of all grades of erosive esophagitis (EE). (1.1)
- Maintaining healing of EE and relief of heartburn. (1.2)
- Treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD). (1.3)

DEXILANT SoluTab delayed-release orally disintegrating tablets (DEXILANT SoluTab) are indicated in adults for:

- Maintaining healing of EE and relief of heartburn. (1.2)
- Treating heartburn associated with GERD. (1.3)

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

Recommended Adult Dosage:

Two 30 mg DEXILANT SoluTab are not interchangeable with one 60 mg DEXILANT capsule. (2.1)

DEXILANT capsules

- Healing of EE: 60 mg once daily for up to 8 weeks. (2.1)
- Maintenance of healed EE: 30 mg once daily for up to 6 months. (2.1)
- Symptomatic non-erosive GERD: 30 mg once daily for 4 weeks. (2.1)

DEXILANT SoluTab

- Maintenance of healed EE: 30 mg once daily for up to 6 months. (2.1)
- Symptomatic non-erosive GERD: 30 mg once daily for 4 weeks. (2.1)

Dosage Adjustment in Adults with Hepatic Impairment for the Healing of EE (2.2):

- Moderate hepatic impairment (Child-Pugh Class B): 30 mg once daily for up to 8 weeks of DEXILANT capsules or DEXILANT SoluTab.
- Severe hepatic Impairment (Child-Pugh Class C): use is not recommended.

Administration Instructions (2.3):

DEXILANT capsules

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

DEXILANT SoluTab

- Take at least 30 minutes before a meal.
- Do not break or cut.
- Place the tablet on the tongue, allow to disintegrate and swallow without water. Do not chew microgranules.
- May also be swallowed whole with water.
- Avoid use of alcohol when taking DEXILANT SoluTab (7)
- See full prescribing information for alternative administration options.

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

- Delayed-release capsules: 30 mg and 60 mg. (3)
- Delayed-release orally disintegrating tablets: 30 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: Symptomatic response with DEXILANT does not preclude the presence of gastric malignancy. (5.1)
- Acute Interstitial Nephritis: Observed in patients taking PPIs. (5.2)
- Cyanocobalamin (Vitamin B-12) Deficiency: Daily long-term use (e.g., longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin. (5.3)
- Clostridium difficile Associated Diarrhea: PPI therapy may be associated with increased risk. (5.4)
- 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. (5.5)
- Hypomagnesemia: Reported rarely with prolonged treatment with PPIs. (5.6)
- Interactions with Diagnostic 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. (5.7, 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 DEXILANT (5.8, 7).

-----ADVERSE REACTIONS-----

Most commonly reported adverse reactions ($\geq 2\%$): diarrhea, abdominal pain, nausea, upper respiratory tract infection, vomiting, and flatulence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals America, Inc. at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or 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.

Revised: 01/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Healing of Erosive Esophagitis

DEXILANT delayed-release capsules (DEXILANT capsules) are indicated in adults for healing of all grades of erosive esophagitis (EE) for up to eight weeks.

1.2 Maintenance of Healed Erosive Esophagitis

DEXILANT capsules and DEXILANT SoluTab delayed-release orally disintegrating tablets (DEXILANT SoluTab) are indicated in adults to maintain healing of EE and relief of heartburn for up to six months.

1.3 Symptomatic Non-Erosive Gastroesophageal Reflux Disease

DEXILANT capsules and DEXILANT SoluTab are indicated in adults for the treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for four weeks.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Adult Dosage

Two 30 mg DEXILANT SoluTab are not interchangeable with one 60 mg DEXILANT capsule [see *Clinical Pharmacology* (12.3)].

Table 1. DEXILANT Capsules Adult Dosing Recommendations

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.

Table 2. DEXILANT SoluTab Adult Dosing Recommendations

Indication	Recommended Dosage Regimen
Maintenance of Healed EE and Relief of Heartburn	One 30 mg tablet once daily*
Symptomatic Non-Erosive GERD	One 30 mg tablet once daily for 4 weeks

*Controlled studies did not extend beyond 6 months.

2.2 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 DEXILANT capsule or DEXILANT SoluTab once daily for up to 8 weeks. The use of DEXILANT capsule or DEXILANT SoluTab 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.

DEXILANT capsules

- Take without regard to food.
- Swallow whole; do not chew.
- For patients who have trouble swallowing capsules, DEXILANT 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.

DEXILANT SoluTab

- Take at least 30 minutes before a meal.
- Do not break or cut.
- Place the tablet on the tongue, allow it to disintegrate, and swallow the microgranules without water. Do not chew the microgranules.
- May also be swallowed whole with water.
- Avoid use of alcohol when taking DEXILANT SoluTab [see *Drug Interactions (7)*].
- Alternatively, the tablet can be administered with water via oral syringe or NG tube (see below).

Administration with Water in an Oral Syringe

1. Place one tablet in an oral syringe and draw up 20 mL of water.
2. Swirl gently to allow for a quick dispersal.
3. After the tablet has dispersed, administer the contents immediately into the mouth. Do not save the water and microgranule mixture for later use.
4. Refill the syringe with approximately 10 mL of water, swirl gently, and administer any remaining contents.
5. Refill the syringe again with approximately 10 mL of water, swirl gently, and administer any remaining contents.

Administration with Water via a NG Tube (≥ 8 French)

1. Place one tablet in a catheter-tip syringe and draw up 20 mL of water.
2. Shake gently to allow for a quick dispersal.
3. After the tablet has dispersed, swirl the catheter-tip syringe gently in order to keep the microgranules from settling, and immediately inject the mixture through the NG tube into the stomach. Do not save the water and microgranule mixture for later use.
4. Refill the catheter-tip syringe with approximately 10 mL of water, shake 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

DEXILANT delayed-release capsules

- 30 mg: strength is an opaque, blue and gray capsule imprinted with TAP and “30”.
- 60 mg: strength is an opaque, blue capsule imprinted with TAP and “60”.

DEXILANT SoluTab delayed-release orally disintegrating tablets

- 30 mg: strength is a white to yellowish-white, round, tablet containing orange to dark brown speckles, with “D30” debossed on one side.

4 CONTRAINDICATIONS

- DEXILANT is 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 DEXILANT, are contraindicated with rilpivirine-containing products [see *Drug Interactions (7)*].

5 WARNINGS AND PRECAUTIONS

5.1 Presence of Gastric Malignancy

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

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 DEXILANT if acute interstitial nephritis develops [see *Contraindications (4)*].

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

5.4 *Clostridium Difficile* Associated Diarrhea

Published observational studies suggest that PPI therapy like DEXILANT 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.

5.5 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), *Adverse Reactions* (6.2)].

5.6 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)].

5.7 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)].

5.8 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)]
- Cyanocobalamin (Vitamin B-12) Deficiency [see *Warnings and Precautions* (5.3)]
- *Clostridium difficile* Associated Diarrhea [see *Warnings and Precautions* (5.4)]
- Bone Fracture [see *Warnings and Precautions* (5.5)]
- Hypomagnesemia [see *Warnings and Precautions* (5.6)]

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.

The safety of DEXILANT capsules was evaluated in 4548 patients in controlled and uncontrolled clinical studies, 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 DEXILANT 30 mg capsules, 2218 patients on DEXILANT 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 DEXILANT capsules than placebo in the controlled studies are presented in Table 3.

Table 3. Common Adverse Reactions in Controlled Studies					
Adverse Reaction	Placebo (N=896) %	DEXILANT 30 mg capsules (N=455) %	DEXILANT 60 mg capsules (N=2218) %	DEXILANT capsules Total (N=2621) %	Lansoprazole 30 mg (N=1363) %
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 DEXILANT therapy 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, pruritus, rash, skin lesion, urticaria

Vascular Disorders: deep vein thrombosis, hot flush, hypertension

Additional adverse reactions that were reported in a long-term uncontrolled study and were considered related to DEXILANT 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.

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval of DEXILANT. 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 DEXILANT 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 DEXILANT and Interactions with Diagnostics

Antiretrovirals	
<i>Clinical Impact:</i>	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.
<i>Intervention:</i>	<u>Rilpivirine-containing products</u>: Concomitant use with DEXILANT is contraindicated [see <i>Contraindications (4)</i>]. See prescribing information. <u>Atazanavir</u>: See prescribing information for atazanavir for dosing information. <u>Nelfinavir</u>: Avoid concomitant use with DEXILANT. See prescribing information for nelfinavir. <u>Saquinavir</u>: See the prescribing information for saquinavir and monitor for potential saquinavir toxicities. <u>Other antiretrovirals</u>: See prescribing information.
Warfarin	
<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.
Methotrexate	
<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 (5.8)</i>].
<i>Intervention:</i>	A temporary withdrawal of DEXILANT may be considered in some patients receiving high-dose methotrexate.
Digoxin	
<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.

Drugs Dependent on Gastric pH for Absorption (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole/itraconazole)	
<i>Clinical Impact:</i>	Dexlansoprazole 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 DEXILANT and MMF. Use DEXILANT with caution in transplant patients receiving MMF. See the prescribing information for other drugs dependent on gastric pH for absorption.
Tacrolimus	
<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.
Interactions with Investigations of Neuroendocrine Tumors	
<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</i> (5.7), <i>Clinical Pharmacology</i> (12.2)].
<i>Intervention:</i>	Temporarily stop DEXILANT 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	
<i>Clinical Impact:</i>	Hyper-response in gastrin secretion in response to secretin stimulation test, falsely suggesting gastrinoma.
<i>Intervention:</i>	Temporarily stop DEXILANT treatment at least 30 days before assessing to allow gastrin levels to return to baseline [see <i>Clinical Pharmacology</i> (12.2)].
False Positive Urine Tests for THC	
<i>Clinical Impact:</i>	There have 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 DEXILANT When Co-Administered with Other Drugs

CYP2C19 or CYP3A4 Inducers	
<i>Clinical Impact:</i>	Decreased exposure of dexlansoprazole when used concomitantly with strong inducers [see <i>Clinical Pharmacology</i> (12.3)].
<i>Intervention:</i>	<u>St. John's Wort, rifampin</u> : Avoid concomitant use with DEXILANT. <u>Ritonavir-containing products</u> : See prescribing information.
CYP2C19 or CYP3A4 Inhibitors	
<i>Clinical Impact:</i>	Increased exposure of dexlansoprazole is expected when used concomitantly with strong inhibitors [see <i>Clinical Pharmacology</i> (12.3)].
<i>Intervention:</i>	<u>Voriconazole</u> : See prescribing information.
Alcohol and DEXILANT SoluTab	
<i>Clinical Impact:</i>	Alcohol may modify the release rate of dexlansoprazole from DEXILANT SoluTab, possibly leading to decreased efficacy.
<i>Intervention:</i>	Avoid alcoholic beverages when taking DEXILANT SoluTab [see <i>Dosage and Administration</i> (2.3)].

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 9 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 DEXILANT and any potential adverse effects on the breastfed child from DEXILANT or from the underlying maternal condition.

Data

When [¹⁴C] 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

Safety and effectiveness of DEXILANT have not been established in pediatric patients.

The use of DEXILANT 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.

8.5 Geriatric Use

Of the total number of patients (n=4548) in clinical studies of DEXILANT, 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 DEXILANT capsules or DEXILANT SoluTab is necessary for patients with mild hepatic impairment (Child-Pugh Class A).

In a study of patients with moderate hepatic impairment (Child-Pugh Class B) who received a single 60 mg DEXILANT 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 adult patients with moderate hepatic impairment (Child-Pugh Class B), the recommended dosage of DEXILANT capsules or DEXILANT SoluTab for the healing of EE is 30 mg once daily for up to 8 weeks [see *Dosage and Administration* (2.2)].

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

10 OVERDOSAGE

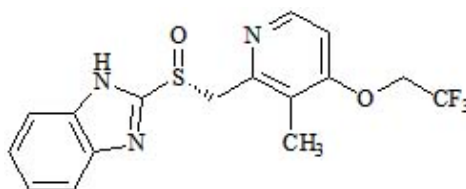
There have been no reports of significant overdose of DEXILANT. Multiple doses of DEXILANT 120 mg and a single dose of DEXILANT 300 mg did not result in death or other severe adverse events. However, serious adverse events of hypertension have been reported in association with twice daily doses of DEXILANT 60 mg. Non-serious adverse reactions observed with twice daily doses of DEXILANT 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 DEXILANT (dexlansoprazole) delayed-release capsules and DEXILANT SoluTab (dexlansoprazole) delayed-release orally disintegrating tablets, a proton pump inhibitor, is (+)-2-[(*R*)-{[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl] methyl} sulfinyl]-1*H*-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:



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 and orally disintegrating tablets. The capsules and tablets contain dexlansoprazole in a mixture of two types of enteric-coated granules with different pH-dependent dissolution profiles [see *Clinical Pharmacology* (12.3)].

DEXILANT 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 (active ingredient) and the following inactive ingredients: sugar spheres, magnesium carbonate, sucrose, low-substituted hydroxypropyl cellulose, titanium dioxide, hydroxypropyl cellulose, hypromellose 2910, talc, methacrylic acid copolymers, polyethylene glycol 8000, triethyl citrate, polysorbate 80, and colloidal silicon dioxide. The components of the capsule shell include the following inactive ingredients: hypromellose, carrageenan and potassium chloride. Based on the capsule shell color, blue contains FD&C Blue No. 2 aluminum lake; gray contains black ferric oxide; and both contain titanium dioxide.

DEXILANT SoluTab delayed-release orally disintegrating tablets are available as 30 mg tablets. Each tablet contains enteric-coated microgranules. The tablet consists of dexlansoprazole (active ingredient) and the following inactive ingredients: lactose monohydrate-microcrystalline cellulose spheres, magnesium carbonate, low-substituted hydroxypropyl cellulose, hydroxypropyl cellulose, hypromellose, talc, titanium dioxide, mannitol, methacrylic acid copolymer, ethyl acrylate methyl methacrylate copolymer, polysorbate 80, glyceryl monostearate, triethyl citrate, anhydrous citric acid, ferric oxide, red; ferric oxide, yellow; polyethylene glycol 8000, methylacrylate methylmethacrylate methacrylic acid copolymer, microcrystalline cellulose, crospovidone, sucralose, strawberry durarome, and magnesium stearate.

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⁺, 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.

12.2 Pharmacodynamics

Antisecretory Activity

The effects of DEXILANT 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 Intra gastric pH on Day 5 After Administration of DEXILANT or Lansoprazole	
DEXILANT 60 mg capsules	Lansoprazole 30 mg
Mean Intra gastric pH	
4.55	4.13
% Time Intra gastric 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 DEXILANT 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* (5.7)].

Enterochromaffin-Like Cell (ECL) Effects

There were no reports of ECL cell hyperplasia in gastric biopsy specimens obtained from 653 patients treated with DEXILANT 30 mg, 60 mg, or 90 mg delayed-release 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)].

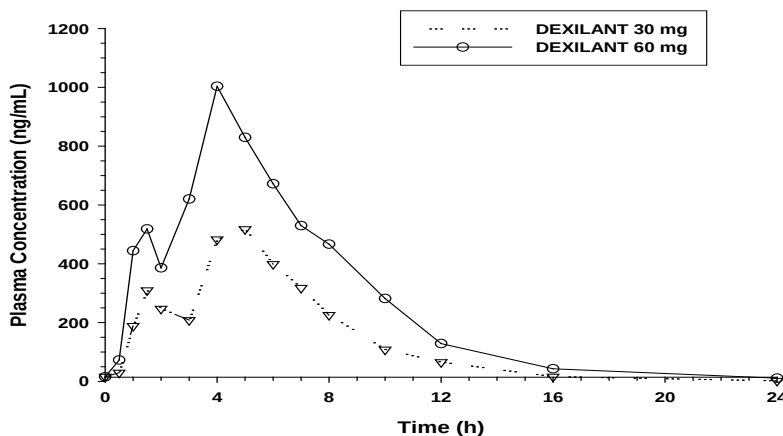
Cardiac Electrophysiology

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 DEXILANT 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 DEXILANT 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 or 60 mg DEXILANT Capsules Once Daily for 5 Days in Healthy 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).

Table 7. Mean (CV%) Pharmacokinetic Parameters for Subjects on Day 5 After Administration of DEXILANT Capsules			
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 DEXILANT 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 DEXILANT 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 DEXILANT 60 mg was administered as an intact capsule [see Dosage and Administration (2.3)].

After oral administration of DEXILANT SoluTab 30 mg tablet to healthy adults under fasting condition, median time (T_{max}) to peak plasma concentrations (C_{max}) of dexlansoprazole was 4 hours and ranged from 1 to 6 hours, the C_{max} was 688 ng/mL (CV of 49%) and AUC was 2866 ng·h/mL (CV of 77%).

The bioavailability (C_{max} and AUC) of dexlansoprazole was similar when DEXILANT SoluTab 30 mg tablets were mixed with water and administered via oral syringe, NG tube, or swallowed intact with water compared to DEXILANT SoluTab 30 mg tablets administered on the tongue, allowed to disintegrate and swallowed without water under fasting conditions in healthy subjects [see Dosage and Administration (2.3)].

Two 30 mg DEXILANT SoluTab are not interchangeable with one 60 mg DEXILANT capsule because systemic exposure is lower, and two 30 mg Dexilant SoluTab are not recommended for the healing of EE [see Indications (1.1), Dosage and Administration (2.1)].

Effect on Food

In food-effect studies in healthy subjects receiving DEXILANT 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)].

In healthy adults, a concomitant administration of a standard high-fat breakfast contained approximately 800 to 1000 total calories, with 50% of calories being derived from fat content delayed the absorption of dexlansoprazole from DEXILANT SoluTab 30 mg tablet resulting in a median $T_{\max}$ of 6 hours and decreased the $C_{\max}$ on average by 38%. Dexlansoprazole AUC was not affected by food [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 DEXILANT capsule, 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/hour, respectively, after five days of 30 or 60 mg once daily administration.

Specific Populations

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 DEXILANT 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 DEXILANT 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 DEXILANT 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 DEXILANT 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 DEXILANT 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 DEXILANT 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 86-97%) when DEXILANT 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 on 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 DEXILANT 30 mg or 60 mg capsules (N=2 to 6 subjects/group), mean dexlansoprazole C_{max} and AUC values were up to two times higher in intermediate compared to extensive metabolizers; in poor metabolizers, mean C_{max} 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/m²) basis of a 50 kg person of average height [1.46 m² 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

Two 30 mg DEXILANT SoluTab are not recommended for the healing of EE [see *Indications and Usage* (1.1), *Clinical Pharmacology* (12.3)].

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-D). Patients were randomized to one of the following three treatment groups: DEXILANT 60 mg capsules daily, DEXILANT 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 8.

Table 8. EE Healing Rates*: All Grades					
Study	Number of Patients (N) [†]	Treatment Group (daily)	Week 4 % Healed	Week 8 [‡] % Healed	(95% CI) for the Treatment Difference (DEXILANT–Lansoprazole) by Week 8
1	657	DEXILANT 60 mg capsules	70	87	(-1.5, 6.1) [§]
	648	Lansoprazole 30 mg	65	85	
2	639	DEXILANT 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.

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

14.2 Maintenance of Healed Erosive Esophagitis

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 DEXILANT 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 DEXILANT capsules remained healed over the six-month time period as confirmed by endoscopy (see Table 9).

Table 9. Maintenance Rates* of Healed EE at Month 6		
Number of Patients (N)[†]	Treatment Group (daily)	Maintenance Rate (%)
125	DEXILANT 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

DEXILANT 60 mg capsules was studied and did not provide additional clinical benefit over DEXILANT 30 mg capsules.

The effect of DEXILANT 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. DEXILANT 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 10*). The majority of patients treated with placebo discontinued due to relapse of EE between month two and month six.

Table 10. Median Percentage of 24 Hour Heartburn-Free Periods of the Maintenance of Healed EE Study						
	Overall Treatment*		Month 1		Month 6	
Treatment Group (daily)	N	Heartburn-Free 24-hour Periods (%)	N	Heartburn-Free 24-hour Periods (%)	N	Heartburn-Free 24-hour Periods (%)
DEXILANT 30 mg capsules	132	96.1 [†]	126	96.7	80	98.3
Placebo	141	28.6	117	28.6	23	73.3

*Secondary efficacy endpoint

[†]Statistically significant vs placebo

14.3 Symptomatic Non-Erosive GERD

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: DEXILANT 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.

DEXILANT 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 11). DEXILANT 60 mg capsules was studied and provided no additional clinical benefit over DEXILANT 30 mg capsules.

Table 11. Median Percentages of 24 Hour Heartburn-Free Periods During the 4 Week Treatment Period of the Symptomatic Non-Erosive GERD Study		
N	Treatment Group (daily)	Heartburn-Free 24-hour Periods (%)
312	DEXILANT 30 mg capsules	54.9*
310	Placebo	18.5

*Statistically significant vs placebo

A higher percentage of patients on DEXILANT 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: DEXILANT 38% versus placebo 15%; on Day 28: DEXILANT 63% versus placebo 40%).

16 HOW SUPPLIED/STORAGE AND HANDLING

DEXILANT delayed-release capsules, 30 mg, are opaque, blue and gray with TAP and “30” imprinted on the capsule and supplied as:

<u>NDC Number</u>	<u>Size</u>
64764-171-11	Unit dose package of 100
64764-171-30	Bottle of 30
64764-171-90	Bottle of 90
64764-171-19	Bottle of 1000

DEXILANT delayed-release capsules, 60 mg, are opaque, blue with TAP and “60” imprinted on the capsule and supplied as:

<u>NDC Number</u>	<u>Size</u>
64764-175-11	Unit dose package of 100
64764-175-30	Bottle of 30
64764-175-90	Bottle of 90
64764-175-19	Bottle of 1000

DEXILANT SoluTab delayed-release orally disintegrating tablets, 30 mg, are white to yellowish-white, round, tablets containing orange to dark brown speckles, with “D30” debossed on one side and supplied as:

<u>NDC Number</u>	<u>Size</u>
64764-177-11	Unit dose package of 100

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 patient 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)*].
- Cyanocobalamin (Vitamin B-12) Deficiency [see *Warnings and Precautions (5.3)*].
- *Clostridium difficile* Associated Diarrhea [see *Warnings and Precautions (5.4)*].
- Bone Fracture [see *Warnings and Precautions (5.5)*].
- Hypomagnesemia [see *Warnings and Precautions (5.6)*].

Drug Interactions

Advise patients to report to their healthcare provider if they are taking high-dose methotrexate [see *Warnings and Precautions (5.8)*].

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.

DEXILANT 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.

DEXILANT SoluTab

- Take at least 30 minutes before a meal.
- Do not break or cut.
- Place the tablet on the tongue, allow it to disintegrate, and swallow the microgranules without water. Do not chew the microgranules.
- May also be swallowed whole with water.
- Avoid use of alcohol when taking DEXILANT SoluTab [see *Drug Interactions (7)*].
- Alternatively, the tablet can be administered with water via oral syringe or NG tube.

MEDICATION GUIDE

**DEXILANT (decks-i-launt)
(dexlansoprazole)
delayed-release capsules
and
DEXILANT SoluTab (decks-i-launt sol-u-tab)
(dexlansoprazole)
delayed-release orally disintegrating tablets**

Read this Medication Guide before you start taking DEXILANT 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.

What is the most important information that I should know about DEXILANT?

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

DEXILANT can cause serious side effects, including:

- **Diarrhea.** DEXILANT 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 proton pump inhibitor 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 DEXILANT 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 DEXILANT.

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

What is DEXILANT?

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

DEXILANT delayed-release capsules (DEXILANT capsules) are used in adults:

- 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 to continue healing of erosive esophagitis and relief of heartburn
- for 4 weeks to treat heartburn related to gastroesophageal reflux disease (GERD)

DEXILANT SoluTab delayed-release orally disintegrating tablets (DEXILANT SoluTab) is used in adults:

- for up to 6 months to continue healing of EE and relief of heartburn
- for 4 weeks to treat heartburn related to 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 DEXILANT is safe and effective in children.

DEXILANT is not effective for symptoms of GERD in children under 1 year of age.

Who should not take DEXILANT?

Do not take DEXILANT if you:

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

What should I tell my doctor before taking DEXILANT?

Before you take DEXILANT, 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 DEXILANT will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if DEXILANT 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 DEXILANT.

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

- Take DEXILANT exactly as prescribed by your doctor.
- Do not change your dose or stop taking DEXILANT without talking to your doctor first.

DEXILANT capsules:

- o Take DEXILANT capsules with or without food.
- o Swallow DEXILANT capsules whole. Do not chew DEXILANT capsules or the granules that are in the capsules.
- o 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 DEXILANT capsules with applesauce.
- o See the “Instructions for Use” at the end of this Medication Guide for instructions on how to mix and give DEXILANT capsules with water using an oral syringe or through a nasogastric tube.

DEXILANT SoluTab

- o DEXILANT SoluTab is a tablet that melts in your mouth without water.
- o Take DEXILANT SoluTab at least 30 minutes before a meal.
- o Do not break or cut DEXILANT SoluTab.
- o Place DEXILANT SoluTab on your tongue until it melts. Without using water, swallow after the tablet melts. Do not chew the granules after the tablet melts.
- o DEXILANT SoluTab may also be swallowed whole with water.
- o See the “Instructions for Use” at the end of this Medication Guide for instructions about how to mix and give DEXILANT SoluTab with water using an oral syringe or through a nasogastric tube.
- If you miss a dose of DEXILANT, take it as soon as you remember. If it is almost time for your next dose, do not take the missed dose. Take your 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 DEXILANT, call your doctor or your poison control center at 1-800-222-1222 right away or go to the nearest hospital emergency room.

What should I avoid while taking DEXILANT SoluTab?

Avoid taking DEXILANT SoluTab with alcohol.

Taking DEXILANT SoluTab with alcohol may affect how DEXILANT SoluTab works.

What are the possible side effects of DEXILANT?

DEXILANT may cause serious side effects, including:

- See “What is the most important information I should know about DEXILANT?”
- **Vitamin B-12 deficiency.** DEXILANT 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 DEXILANT 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:

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

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

The most common side effects of DEXILANT 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 DEXILANT:

- rash
- face swelling
- throat tightness
- difficulty breathing

Your doctor may stop DEXILANT 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 DEXILANT. 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 DEXILANT?

- Store DEXILANT at room temperature between 68°F to 77°F (20°C to 25°C).

Keep DEXILANT and all medicines out of the reach of children.

General information about the safe and effective use of DEXILANT

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use DEXILANT for a condition for which it was not prescribed. Do not give DEXILANT 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 DEXILANT. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about DEXILANT that is written for health professionals.

For more information, go to www.DEXILANT.com or call 1-877-825-3327.

What are the ingredients in DEXILANT capsules and DEXILANT SoluTab?

Active ingredient: dexlansoprazole.

DEXILANT capsules:

Inactive ingredients: sugar spheres, magnesium carbonate, sucrose, low-substituted hydroxypropyl cellulose, titanium dioxide, hydroxypropyl cellulose, hypromellose 2910, talc, methacrylic acid copolymers, polyethylene glycol 8000, triethyl citrate, polysorbate 80, and colloidal silicon dioxide. The capsule shell is made of hypromellose, carrageenan and potassium chloride. Based on the capsule shell color, blue contains FD&C Blue No. 2 aluminum lake; gray contains black ferric oxide; and both contain titanium dioxide.

DEXILANT SoluTab:

Inactive ingredients: lactose monohydrate-microcrystalline cellulose spheres, magnesium carbonate, low-substituted hydroxypropyl cellulose, hydroxypropyl cellulose, hypromellose, talc, titanium dioxide, mannitol, methacrylic acid copolymer, ethyl acrylate methyl methacrylate copolymer, polysorbate 80, glyceryl monostearate, triethyl citrate, anhydrous citric acid, ferric oxide, red; ferric oxide, yellow; polyethylene glycol 8000, methylacrylate methylmethacrylate methacrylic acid copolymer, microcrystalline cellulose, crospovidone, sucralose, strawberry durarome, and magnesium stearate.

Instructions for Use

**DEXILANT (decks-i-launt)
(dexlansoprazole)
delayed-release capsules
and
DEXILANT SoluTab (decks-i-launt sol-u-tab)
(dexlansoprazole)
delayed-release orally disintegrating tablets**

DEXILANT delayed-release capsules (DEXILANT capsules)

Taking DEXILANT 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 DEXILANT 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 DEXILANT capsules with water through a nasogastric tube (NG tube):

For people who have an NG tube that is **size 16 French or larger**, DEXILANT 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 that goes 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.

DEXILANT SoluTab delayed-release orally disintegrating tablets (DEXILANT SoluTab)

Giving DEXILANT SoluTab with water using an oral syringe:

1. Put 1 tablet in an oral syringe and draw up 20 mL of water into the oral syringe.
2. Gently swirl the oral syringe to mix the tablet and the water.
3. After the tablet is mixed in the water, place the tip of the oral syringe in your mouth. Give the medicine right away. Do not save the tablet and water mixture for later use.
4. Refill the syringe with about 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.
5. Repeat step 4.

Giving DEXILANT SoluTab with water through a nasogastric tube (NG tube):

For people who have an NG tube that is **size 8 French or larger**, DEXILANT SoluTab may be given as follows:

1. Put 1 tablet in a catheter-tip syringe and draw up 20 mL of water.
2. Gently swirl the catheter-tip syringe to mix the tablet and the water.
3. After the tablet is mixed in the water, swirl the catheter-tip syringe gently in order to keep the particles from settling.
4. Connect the catheter-tip syringe to the NG tube.
5. Give the mixture right away through the NG tube that goes into the stomach. Do not save the tablet and water mixture for later use.
6. Refill the catheter-tip syringe with about 10 mL of water and swirl gently. Flush the NG tube with water.
7. Repeat step 6.

How should I store DEXILANT?

- Store DEXILANT at room temperature between 68°F to 77°F (20°C to 25°C).

Keep DEXILANT and all medicines out of the reach of children.

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

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