PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# [Pr]DEXILANT®

Dexlansoprazole

Capsule (delayed release), 30 mg and 60 mg, Nasogastric and Oral

Proton Pump Inhibitor

Takeda Canada Inc.
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**RECENT MAJOR LABEL CHANGES**

| | |
|---|---|
| 7.0 Warnings and Precautions, Immune | 03/2023 |

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**Sections or subsections that are not applicable at the time of authorization are not listed.**

## PART I: HEALTH PROFESSIONAL INFORMATION

## 1 INDICATIONS

DEXILANT (dexlansoprazole delayed release capsules) is indicated for:

- healing of all grades of erosive esophagitis (EE) for up to 8 weeks in patients 12 years of age and older.
- maintaining healing of erosive esophagitis for up to 4 months in adolescents 12 to 17 years of age and up to 6 months in adults.
- the treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for 4 weeks in patients 12 years of age and older.

### 1.1 Pediatrics

- **Pediatrics (12 to 17 years of age)**: Based on the data submitted and reviewed by Health Canada, the safety and efficacy of DEXILANT in pediatric patients aged 12 to 17 years has been established. Therefore, Health Canada has authorized all indications for pediatric use in this age group. See 14.1 Clinical Trials by Indication.
- **Pediatrics (<12 years of age)**: Based on the data submitted and reviewed by Health Canada, the safety and efficacy of DEXILANT in pediatric patients aged less than 12 years has not been established; therefore, Health Canada has not authorized an indication for pediatric use in this age group. See 7.1.3 Pediatrics.

### 1.2 Geriatrics

- **Geriatrics (>65 years of age)**: Based on the data submitted and reviewed by Health Canada, the safety and efficacy of DEXILANT in geriatric patients has been established. Therefore, Health Canada has authorized all indications for geriatric use. No dosage adjustment is necessary for elderly patients. See 7.1.4 Geriatrics.

## 2 CONTRAINDICATIONS

- Dexlansoprazole is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Dexlansoprazole is contraindicated with co-administration of rilpivirine. See 7 WARNINGS AND PRECAUTIONS and 9.4 Drug-Drug Interactions.

## 4 DOSAGE AND ADMINISTRATION

### 4.1 Dosing Considerations

- Patients should use the lowest dose and shortest duration of proton pump inhibitor (PPI) therapy appropriate to the condition being treated.
- Withdrawal of long-term PPI therapy can lead to aggravation of acid related symptoms and may result in rebound acid hypersecretion.

### 4.2 Recommended Dose and Dosage Adjustment

| Indication | Recommended Dose, Route of administration | Frequency |
|---|---|---|
| Healing of Erosive Esophagitis | 60 mg, Oral or Nasogastric | Once daily for up to 8 weeks |
| Maintenance of Healed Erosive Esophagitis | 30 mg [a], Oral or Nasogastric | Once daily for up to 6 months in adults and 4 months in adolescents (12 to 17 years)[b] |
| Symptomatic Non-Erosive Gastroesophageal Reflux Disease (GERD) | 30 mg, Oral or Nasogastric | Once daily for 4 weeks |

[a] In patients who had moderate or severe erosive esophagitis, a maintenance dose of 60 mg may be used.
[b] Controlled studies did not extend beyond 6 months in adults, and beyond 4 months in adolescents 12 to 17 years of age.

- No dosage adjustment for DEXILANT is necessary for patients with mild hepatic impairment (Child-Pugh Class A). DEXILANT 30 mg should be considered for patients with moderate hepatic impairment (Child-Pugh Class B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).
- No dosage adjustment is necessary for elderly patients or for patients with renal impairment.
- Health Canada has not authorized an indication for pediatric use in patients less than 12 years of age. See 7.1.3 Pediatrics.

### 4.4 Administration

DEXILANT can be taken without regard to food or the timing of food.

DEXILANT should be swallowed whole with plenty of water.

- Alternatively, DEXILANT capsules can be opened and administered as follows:
- Administration with Applesauce
  1. Place one tablespoon 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.
- 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. Repeat step 5.
- Administration with Water via a Nasogastric 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 syringe gently in order to keep the granules from settling, and immediately inject the mixture through the nasogastric tube into the stomach. Do not save the water and granule mixture for later use.
4. Refill the syringe with 10 mL of water, swirl gently, and flush the tube.
5. Repeat step 4.

### 4.5 Missed Dose

If a capsule is missed at its usual time, it should be taken as soon as possible. But if it is too close to the time of the next dose, only the prescribed dose should be taken at the appointed time. A double dose should not be taken.

## 5 OVERDOSAGE

There have been no reports of significant overdose of DEXILANT. Dexlansoprazole is not expected to be removed from the circulation by hemodialysis.

For management of a suspected drug overdose, contact your regional poison control centre.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Dosage Forms, Strengths, Composition and Packaging**

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|---|---|---|
| Oral, Nasogastric | Capsule (delayed release)<br>30 mg, 60 mg<br>Dexlansoprazole | Capsule: colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose 2910, low-substituted hydroxypropyl cellulose, magnesium carbonate, methacrylic acid copolymer, polyethylene glycol 8000, polysorbate 80, sucrose, sugar spheres, talc, titanium dioxide, and triethyl citrate.<br>Capsule shell: carrageenan, hypromellose 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 is supplied as a dual delayed release formulation in capsules for oral administration using Dual Delayed Release technology. The capsules contain dexlansoprazole in a mixture of two types of enteric-coated granules with different pH-dependent dissolution profiles. One type of granule is designed to release dexlansoprazole after the granules reach the proximal small intestine; the second type of granule is designed to release dexlansoprazole in the distal region of the small intestine, generally several hours later.

DEXILANT is provided in high-density polyethylene (HDPE) bottles in 90 count configurations. Each 30 mg capsule is opaque, blue and gray with TAP and “30” imprinted on the capsule and each 60 mg capsule is opaque, blue with TAP and “60” imprinted on the capsule.

## 7 WARNINGS AND PRECAUTIONS

**General**

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

*Antibiotic Combination Therapy:* Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *Clostridia*. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

*Clostridium Difficile-Associated Diarrhea:* Decreased gastric acidity due to any means, PPIs, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with PPIs can lead to an increased risk of gastrointestinal infections such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

An increased risk for *Clostridium difficile* infection (CDI) and *Clostridium difficile*-associated diarrhea (CDAD) has been observed in association with PPI use in several observational studies. CDI/CDAD should be considered in the differential diagnosis for diarrhea that does not improve. Additional risk factors for CDI and CDAD include recent hospitalization, the use of antibiotics, old age and the presence of co-morbidities.

Patients should be prescribed PPIs at the lowest dose and for the shortest duration required for the condition being treated and be reassessed to ascertain whether continued PPI therapy remains beneficial.

*Concomitant Use 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. A temporary withdrawal of the PPI may be considered in some patients receiving treatments with high dose methotrexate. See 9.4 Drug-Drug Interactions.

**Carcinogenesis and Mutagenesis**

Dexlansoprazole has shown genotoxic and carcinogenic potential in experimental animals. See 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity.

**Drug Interactions with Antiretroviral Drugs**

PPIs have been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known. A change in gastric pH may change the absorption of the antiretroviral drug. Other possible mechanisms are via CYP2C19. See 9.4 Drug-Drug Interactions.

*Rilpivirine*: Co-administration is contraindicated due to significant decrease in rilpivirine exposure and loss of therapeutic effect. See 2 CONTRAINDICATIONS.

*Atazanavir and Nelfinavir:* Co-administration with atazanavir or nelfinavir is not recommended due to decreased atazanavir and nelfinavir exposure (see the REYATAZ® and VIRACEPT® Product Monographs).

If the combination of DEXILANT with atazanavir is judged unavoidable, close clinical monitoring is recommended in combination with the use of 400 mg atazanavir/100 mg ritonavir dose; the dose of DEXILANT should not exceed an equivalent dose of omeprazole of 20 mg daily (see REYATAZ® Product Monograph).

*Saquinavir:* If DEXILANT is co-administered with saquinavir/ritonavir, caution and monitoring for potential saquinavir toxicities, including gastrointestinal symptoms, increased triglycerides, deep vein thrombosis and QT prolongation, are recommended. Dose reduction of saquinavir should be considered from the safety perspective for individual patients (see INVIRASE® Product Monograph).

**Endocrine and Metabolism**

*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. Hypomagnesemia may lead to hypocalcemia and/or hypokalemia. See 8 ADVERSE REACTIONS. In most patients, treatment of hypomagnesemia (and hypomagnesemia associated hypocalcemia and/or hypokalemia) 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 8 ADVERSE REACTIONS.

The chronic use of PPIs may lead to hypomagnesemia.

*Cyanocobalamin (Vitamin B12) Deficiency:* The prolonged use of PPIs may impair the absorption of protein-bound Vitamin B12 and may contribute to the development of cyanocobalamin (Vitamin B12) deficiency.

**Gastrointestinal**

Long-term use of DEXILANT is associated with an increased risk of fundic gland polyps, especially beyond one year. See 8 ADVERSE REACTIONS. Most fundic gland polyps are asymptomatic. Use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

**Genitourinary**

Testicular interstitial cell adenoma occurred in 1 of 30 rats treated with 50 mg/kg/day of lansoprazole (13 times the recommended human dose based on body surface area) in a one-year toxicity study. See 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity.

These changes are associated with endocrine alterations which have not been, to date, observed in humans.

**Hepatic/Biliary/Pancreatic**

No dosage adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). A maximum daily dose of 30 mg should be considered for patients with moderate hepatic impairment (Child-Pugh Class B). No studies have been conducted in patients with severe hepatic impairment. See

10.3 Pharmacokinetics, Special Populations and Conditions.

**Immune**

*Severe Cutaneous Adverse Reactions:* Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) and erythema multiforme have been reported in association with the use of PPIs. Discontinue dexlansoprazole at the first signs or symptoms of SCARs or other signs of hypersensitivity and consider further evaluation. At the time of prescription, patients should be informed of the signs and symptoms, and advised to monitor closely for skin reactions. See 8.5 Post-Market Drug Reactions.

*Subacute cutaneous lupus erythematosus*: Subacute cutaneous lupus erythematosus (SCLE) has been reported with the use of PPIs. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping DEXILANT. The occurrence of SCLE with previous PPI treatment may increase the risk of SCLE with other PPIs. See 8.5 Post-Market Adverse Drug Reactions.

**Monitoring and Laboratory Tests**

During treatment with antisecretory drugs, chromogranin A (CgA) increases due to decreased gastric acidity. Increased CgA levels may interfere with investigations for neuroendocrine tumours. To avoid this interference, DEXILANT treatment should be stopped 14 days before CgA measurements. See 9.4 Drug-Drug Interactions.

**Musculoskeletal**

*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 condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines. See 4 DOSAGE AND ADMINISTRATION and 8 ADVERSE REACTIONS.

**Renal**

No dosage adjustment is necessary for patients with renal impairment. See 10.3 Pharmacokinetics, Special Populations and Conditions.

**Skin**

See 7 WARNINGS AND PRECAUTIONS - Immune

### 7.1 Special Populations

#### 7.1.1 Pregnant Women

There are no adequate or well-controlled studies in pregnant women with DEXILANT. Exposure in clinical trials was very limited. DEXILANT should not be administered to pregnant women unless the expected benefits outweigh the potential risks. See 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology.

### 7.1.2 Breast-feeding

It is not known whether DEXILANT (dexlansoprazole) is excreted in human milk. However, lansoprazole (the racemate) and its metabolites are excreted in the milk of rats. As many drugs are excreted in human milk, DEXILANT should not be given to nursing mothers unless its use is considered essential. In this case, nursing should be avoided.

### 7.1.3 Pediatrics

**Pediatrics (<12 years of age):** Based on the data submitted and reviewed by Health Canada, the safety and efficacy of DEXILANT in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use in children under 12 years of age.

DEXILANT should not be used in pediatric patients less than one year of age because lansoprazole (the racemic mixture) was not effective for the treatment of symptomatic GERD in a multicenter, double-blind controlled trial. In addition, toxicology studies with lansoprazole have shown heart valve thickening and bone changes in juvenile rats. See 16 NON-CLINICAL TOXICOLOGY, Juvenile Animal Toxicity Data.

**Pediatrics (12 to 17 years of age):** DEXILANT is indicated for adolescents 12 to 17 years of age, and is supported by evidence from adequate and well-controlled studies of dexlansoprazole in adults, and by additional efficacy, safety and pharmacokinetic data in adolescents 12 to 17 years of age for the treatment of heartburn associated with symptomatic non-erosive GERD, healing of all grades of EE, and maintenance of healed EE. See 8.2.1 Clinical Trial Adverse Reactions - Pediatrics, 10.3 Pharmacokinetics, Special Populations and Conditions and 14 CLINICAL TRIALS.

### 7.1.4 Geriatrics

**Geriatrics (>65 years of age):** In clinical studies of DEXILANT, 11% of patients were aged 65 years and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. No dosage adjustment is necessary for elderly patients. See 10.3 Pharmacokinetics, Special Populations and Conditions.

Benefits of use of PPIs should be weighed against the increased risk of fractures as patients in this category (> 71 years of age) may already be at high risk for osteoporosis-related fractures. If the use of PPIs is required, they should be managed carefully according to established treatment guidelines. See 7 WARNINGS AND PRECAUTIONS, Musculoskeletal and 8 ADVERSE REACTIONS.

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

The most common adverse drug reactions (occurring in at least 1% of subjects) reported in adult patients treated with DEXILANT in placebo and positive-controlled trials were diarrhea, abdominal pain, headache, nausea, flatulence, and constipation. The adverse reaction profile observed in adolescent patients (12 to 17 years of age) was similar to that of adults.

### 8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be

compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of DEXILANT was evaluated in 4548 patients in controlled and uncontrolled clinical studies (30 mg, 60 mg, and 90 mg), including 863 patients treated for at least 6 months and 282 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 erosive esophagitis, maintenance of healed erosive esophagitis, and symptomatic GERD, which included 896 patients on placebo, 2621 patients on DEXILANT 30 mg or 60 mg and 1363 patients on lansoprazole 30 mg.

The following adverse events were reported to have a possible or definite treatment-relationship to DEXILANT in 1% or more of the treated patients in placebo and positive-controlled clinical trials (Tables 1 and 2, respectively). Numbers in parentheses indicate the percentage of the adverse events reported.

**Table 1 - Incidence of Possibly or Definitely Treatment-Related Adverse Events in Placebo Controlled Studies**

| **Body System**<br>Adverse Event | **DEXILANT 30 mg and 60 mg (N = 1399) n (%)** | **Placebo (N = 896) n (%)** |
|---|---|---|
| **Gastrointestinal disorders** | | |
| Diarrhea | 52 (3.7) | 17 (1.9) |
| Abdominal Pain | 37 (2.6) | 14 (1.6) |
| Nausea | 31 (2.2) | 16 (1.8) |
| Flatulence | 25 (1.8) | 5 (0.6) |
| Constipation | 15 (1.1) | 9 (1.0) |
| **Nervous system disorders** | | |
| Headache | 31 (2.2) | 21 (2.3) |

**Table 2 - Incidence of Possibly or Definitely Treatment-Related Adverse Events in Active Controlled Clinical Trials**

| **Body System**<br>Adverse Event | **DEXILANT 60 mg and 90 mg (N = 1374) n (%)** | **Lansoprazole 30 mg (N = 1363) n (%)** |
|---|---|---|
| **Gastrointestinal disorders** | | |
| Diarrhea | 44 (3.2) | 28 (2.1) |
| Abdominal pain | 21 (1.5) | 19 (1.4) |
| Nausea | 14 (1.0) | 18 (1.3) |
| **Nervous system disorders** | | |
| Headache | 16 (1.2) | 19 (1.4) |

In placebo-controlled studies, gastrointestinal adverse reactions other than constipation occurred at a

higher incidence for DEXILANT than placebo. In active-controlled studies, diarrhea occurred at a higher incidence for DEXILANT than lansoprazole. The incidence of other common adverse reactions for DEXILANT were similar to or lower than placebo or lansoprazole.

### 8.2.1 Clinical Trial Adverse Reactions – Pediatrics

The safety of DEXILANT was evaluated in controlled and single-arm clinical trials including 166 adolescents, 12 to 17 years of age for the treatment of symptomatic non-erosive GERD, healing of EE, maintenance of healed EE and relief of heartburn. See 14.1 Clinical Trials by Indication.

The adverse reaction profile was similar to that of adults. The most common adverse reactions that occurred in ≥ 5% of patients were headache, abdominal pain, diarrhea, nasopharyngitis and oropharyngeal pain.

### 8.3 Less Common Clinical Trial Adverse Reactions

Other adverse reactions that were reported for DEXILANT (30 mg, 60 mg or 90 mg) in controlled studies at an incidence of less than 1% are listed below by body system:

| | |
|---|---|
| Blood and Lymphatic System Disorders: | anemia, lymphadenopathy |
| Cardiac Disorders: | acute myocardial infarction, angina, arrhythmia, bradycardia, edema, palpitations, 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, 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, paresthesia oral, proctitis, rectal hemorrhage, vomiting |
| 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, upper respiratory tract infection, viral infection, vulvo-vaginal infection |
| Injury, Poisoning and Procedural Complications: | 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 increased |
| 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, memory impairment, migraine, 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, dyspnoea, 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 for DEXILANT (60 mg or 90 mg) in a long-term uncontrolled study included: anaphylaxis, auditory hallucination, B-cell lymphoma, bursitis, central obesity, cholecystitis acute, decreased hemoglobin, dehydration, diabetes mellitus, dysphonia, epistaxis, folliculitis, gout, herpes zoster, hyperglycemia, hyperlipidemia, hypothyroidism, increased neutrophils, MCHC decreased, neutropenia, oral soft tissue disorder, rectal tenesmus, restless legs syndrome, somnolence, thrombocythemia, tonsillitis.

### 8.5 Post-Market Adverse Reactions

Adverse reactions have been identified during post-marketing surveillance of DEXILANT. As 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, fundic gland polyps (FGPs)[†], pancreatitis, microscopic colitis |
| 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 (SJS), subacute cutaneous lupus erythematosus (SCLE)†, toxic epidermal necrolysis (TEN) (some fatal), DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms) (some fatal), Acute generalized exanthematous pustulosis (AGEP), Erythema multiforme |
| Metabolism and Nutritional Disorders: | hypomagnesemia, hypocalcemia*, hypokalemia*, hyponatremia |
| Musculoskeletal and Connective Tissue: | osteoporosis and osteoporosis-related fractures |
| Nervous System Disorders: | cerebrovascular accident, transient ischaemic attack |
| Renal and Urinary Disorders: | acute renal failure, Tubulointerstitial nephritis (TIN) |
| Respiratory, Thoracic and Mediastinal Disorders: | pharyngeal edema, throat tightness |
| Skin and Subcutaneous Tissue Disorders**: | generalized rash, leucocytoclastic vasculitis |

* May be related to the occurrence of hypomagnesemia
† For further information, see 7 WARNINGS AND PRECAUTIONS
** Refer also to Immune System Disorders

## 9 DRUG INTERACTIONS

### 9.2 Drug Interactions Overview

The 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 CYP enzyme system including hydroxylation mainly by CYP2C19, and oxidation to the sulfone by CYP3A4. Clinical drug-drug interaction studies with diazepam, phenytoin, and theophylline demonstrated that the systemic exposures of these drugs were not altered. The combined results from these interaction studies suggest that the administration of multiple QD oral doses of dexlansoprazole MR does not affect the enzyme activity of CYP2C19, CYP2C9, or CYP1A2 in humans. The results of a clinical drug-drug interaction study with clopidogrel indicated that multiple-dose administration with dexlansoprazole 60 mg capsules did not significantly reduce the antiplatelet activity of clopidogrel. In addition, multiple oral doses of dexlansoprazole MR 90-mg capsules did not alter PK and anticoagulant activity of warfarin. Dexlansoprazole causes long lasting inhibition of gastric acid secretion. Therefore, dexlansoprazole may interfere with absorption of drugs where gastric pH is an important determinant of the bioavailability (e.g. Ampicillin esters, digoxin, iron salts, ketoconazole).

Other: Generally, daily treatment with any acid-blocking medicines over a long time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin caused by hypo- or achlorhydria. Rare cases of cyanocobalamin deficiency under acid-blocking therapy have been reported in the literature and should be considered if respective clinical symptoms are observed.

### 9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

**Table 3 - Established or Potential Drug-Drug Interactions**

| Concomitant Drug Name | Source of Evidence | Effect | Clinical comment |
|---|---|---|---|
| Antiretroviral Drugs | C | ↓ rilpivirine, atazanavir, nelfinavir<br>↑saquinavir | See 7 WARNINGS AND PRECAUTIONS, Drug Interactions with Antiretroviral Drugs.<br>*Rilpivirine:* Co-administration is contraindicated due to significant decrease in rilpivirine exposure and loss of therapeutic effect.<br>See 2 CONTRAINDICATIONS.<br>*Atazanavir:* Co-administration of DEXILANT with atazanavir is not recommended. Concomitant administration of omeprazole (20 or 40 mg once daily) substantially reduced plasma $C_{max}$ and AUC of atazanavir in healthy volunteers administered atazanavir or atazanavir/ritonavir (see REYATAZ® Product Monograph).<br>*Nelfinavir:* Co-administration of DEXILANT with nelfinavir is not recommended. Concomitant administration of omeprazole (40 mg daily) with nelfinavir (1250 mg twice daily) markedly reduced the AUC and $C_{max}$ for nelfinavir (by 36% and 37%, respectively) and its active metabolite M8 (by 92% and 89%, respectively) (see VIRACEPT® Product Monograph).<br>*Saquinavir:* Co-administration of saquinavir requires caution and monitoring, along with potential dose reduction of saquinavir, due to increased saquinavir exposure and thus the risk of saquinavir-related toxicities (see the INVIRASE® Product Monograph).<br>Concomitant administration of omeprazole (40 mg daily) with saquinavir/ritonavir (1000/100 mg twice daily) increased saquinavir AUC by 82% and $C_{max}$ by 75%. |
| Clopidogrel | CT | No clinically important effect | Concomitant administration of dexlansoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition. No dose adjustment of |

| Concomitant Drug Name | Source of Evidence | Effect | Clinical comment |
|---|---|---|---|
| | | | clopidogrel is necessary when administered with an approved dose of DEXILANT.<br><br>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 (n=40), for 9 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.<br><br>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 clinical significance of this finding is not clear. |
| Antacids | C | In studies of sucralfate administered concomitantly with lansoprazole: AUC ↓, $C_{max}$ ↓ | No formal drug-drug interaction studies were conducted with DEXILANT and antacids. Drug-drug interactions studies were performed with the racemate lansoprazole and antacids. Simultaneous administration of lansoprazole with aluminum and magnesium hydroxide or magaldrate results in lower peak plasma levels, but does not significantly reduce bioavailability. Antacids may be used concomitantly if required. In clinical trials, antacids were administered concomitantly with lansoprazole delayed-release capsules. In a single-dose crossover study when 30 mg of lansoprazole was administered concomitantly with one gram of sucralfate in healthy volunteers, absorption of lansoprazole was delayed and its bioavailability was reduced. The value of lansoprazole AUC was reduced by 17% and that for $C_{max}$ was reduced by 21%. In a similar study when 30 mg of lansoprazole was administered concomitantly with 2 grams of sucralfate, lansoprazole AUC and $C_{max}$ were reduced by 32% and 55%, respectively. When lansoprazole dosing occurred 30 minutes prior to sucralfate administration, $C_{max}$ was reduced by only 28% and there was no statistically significant difference in lansoprazole AUC. Therefore, lansoprazole should be administered at least 30 |

| Concomitant Drug Name | Source of Evidence | Effect | Clinical comment |
|---|---|---|---|
| | | | minutes prior to sucralfate. It would be expected that similar results would be seen with DEXILANT. |
| Methotrexate | C | - | Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted. 7 WARNINGS AND PRECAUTIONS, General, Concomitant Use with Methotrexate. |
| Tacrolimus | C | ↑ whole blood levels | Concomitant administration of dexlansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19. |
| Theophylline | CT | No established clinical effect | Although a study of the use of concomitant theophylline and dexlansoprazole did not reveal any changes in the pharmacokinetics or pharmacodynamics of theophylline, individual patients should monitor their theophylline level while taking the two drugs concomitantly. |
| Warfarin | C, CT | ↑ INR and PT | In a study of 20 healthy subjects, co-administration of DEXILANT 90 mg once daily for 11 days with a single 25 mg oral dose of warfarin on day 6 did not result in any significant differences in the pharmacokinetics of warfarin or INR compared to administration of warfarin with placebo. However, there have been reports of increased INR and prothrombin time (PT) in patients receiving PPIs and warfarin concomitantly. Patients treated with PPIs and warfarin concomitantly may need to be monitored for increases in INR and PT. |

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical; INR = International normalized ratio

**Drugs with pH-Dependent Absorption Pharmacokinetics**

It is theoretically possible that DEXILANT may interfere with the absorption of other drugs where gastric pH is an important determinant of oral bioavailability (e.g., Ampicillin esters, digoxin, iron salts, ketoconazole).

**Cytochrome P450 Interactions**

DEXILANT is metabolized, in part, by CYP2C19 and CYP3A4. See 10.3 Pharmacokinetics, Metabolism.

*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).

### 9.5 Drug-Food Interactions

DEXILANT can be taken without regard to food or timing of food. See 10.3 Pharmacokinetics.

### 9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

### 9.7 Drug-Laboratory Test Interactions

During treatment with antisecretory drugs, Chromogranin A (CgA) increases due to decreased gastric acidity. Increased CgA levels may interfere with investigations for neuroendocrine tumours. To avoid this interference, DEXILANT treatment should be stopped 14 days before CgA measurements. See 10.2 Pharmacodynamics.

## 10 CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

DEXILANT is a PPI that suppresses gastric acid secretion by specific inhibition of the ($H^+$, $K^+$)-ATPase in the gastric parietal cell. By acting specifically on the proton pump, DEXILANT blocks the final step of acid production.

### 10.2 Pharmacodynamics

*Antisecretory Activity:* The effects of DEXILANT 60 mg (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 4.

**Table 4 - Effect on 24-Hour Intragastric pH on Day 5 After Administration of DEXILANT or Lansoprazole**

| **DEXILANT 60 mg** | **Lansoprazole 30 mg** |
|---|---|
| **Mean Intragastric pH** | |
| 4.55* | 4.13 |
| **% Time Intragastric pH > 4 (hours)** | |
| 71*<br>(17 hours) | 60<br>(14 hours) |

* p value <0.05 versus lansoprazole.

In experimental animals, dexlansoprazole was more potent than lansoprazole in the suppression of basal and stimulated gastric acid secretion across five studies in pylorus-stimulated Sprague Dawley (SD) rats. In studies of basal secretion, histamine 2HCl-, bethanechol chloride-, pentagastrin- and 2 deoxy D glucose-stimulated secretion, lansoprazole demonstrated potency values which were 63, 50, 83, 31 and 63%, respectively, of those seen with dexlansoprazole. Lansoprazole was less potent and demonstrated a potency value which was 45% of that seen with dexlansoprazole following histamine-stimulated gastric acid secretion in Heidenham pouch male dogs.

*Pharmacodynamic Properties:* During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA levels may interfere with investigations for neuroendocrine tumours. Available published evidence suggests that PPIs should be discontinued 14 days prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range. See 7 WARNINGS AND PRECAUTIONS.

The effect of DEXILANT on serum gastrin concentrations was evaluated in approximately 3460 patients in clinical trials up to 8 weeks and in 1025 patients for up to 6 to 12 months. The mean fasting gastrin concentrations increased from baseline during treatment with DEXILANT 30 mg and 60 mg doses. In general, in patients treated for more than 6 months, mean serum gastrin levels increased during approximately the first 3 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

Enterochromaffin-Like Cell (ECL) Effects: There were no reports of ECL cell hyperplasia in gastric biopsy specimens obtained from 857 patients treated with DEXILANT 30 mg, 60 mg or 90 mg for up to 12 months. See 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity.

In male SD rats, dexlansoprazole was more potent than lansoprazole in suppression of lesion formation and alimentary tract injury across three studies. In studies examining indomethacin-induced gastric mucosal lesions, mepirizole-induced duodenal mucosal lesions and reflux esophagitis, lansoprazole demonstrated potency values which were 30, 29 and 37%, respectively, of those seen with dexlansoprazole.

**Cardiac electrophysiology**

A study was conducted to assess the potential of DEXILANT to prolong the QT/$QT_c$ interval in healthy adult subjects. DEXILANT doses of 90 mg or 300 mg did not delay cardiac repolarization compared to placebo. The positive control (moxifloxacin) produced statistically significantly greater mean maximum and time-averaged QT/$QT_c$ intervals compared to placebo.

### 10.3 Pharmacokinetics

**Table 5 - Mean (CV %) Pharmacokinetic Parameters for Healthy Adult Subjects on Day 5 After Administration of DEXILANT**

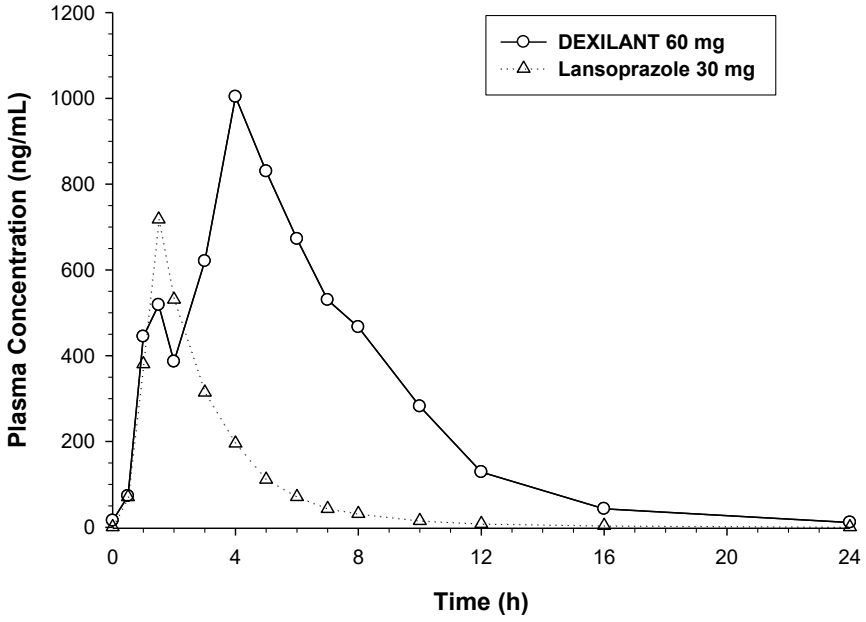
| Dose (mg) | $C_{max}$ (ng/mL) | $t_{max}$[b] (h) | $t_{1/2}$[a] (h) | $AUC_{24}$ (ng·h/mL) | CL/F (L/h) | $V_z/F$ |
|---|---|---|---|---|---|---|
| 30 | 658 (40%) (N=44) | 4.98 (0.98-7.98) (N=44) | 1.49 (N=43) | 3275 (47%) (N=43) | 11.4 (48%) (N=43) | 25.7 (49%) (N=43) |

| Dose (mg) | $C_{max}$ (ng/mL) | $t_{max}$[b] (h) | $t_{1/2}$[a] (h) | $AUC_{24}$ (ng·h/mL) | CL/F (L/h) | $V_z$/F |
|---|---|---|---|---|---|---|
| 60 | 1397 (51%) (N=79) | 4 (1-12) (N=79) | 1.54 (N=73) | 6529 (60%) (N=73) | 11.6 (46%) (N=41) | 33.8 (89%) (N=41) |

[a] Harmonic mean
[b] Median (min-max)

Dexlansoprazole is eliminated with a half-life of approximately 1 to 2 hours in healthy subjects (see Table 5) and in patients with symptomatic GERD. No accumulation of dexlansoprazole occurs after multiple, once daily doses of DEXILANT 30 mg or 60 mg. The formulation of DEXILANT utilizing Dual Delayed Release technology results in a dexlansoprazole plasma concentration-time profile with two distinct peaks; the first peak occurs 1 to 2 hours after administration, followed by a second peak within 4 to 5 hours (see Figure 1).

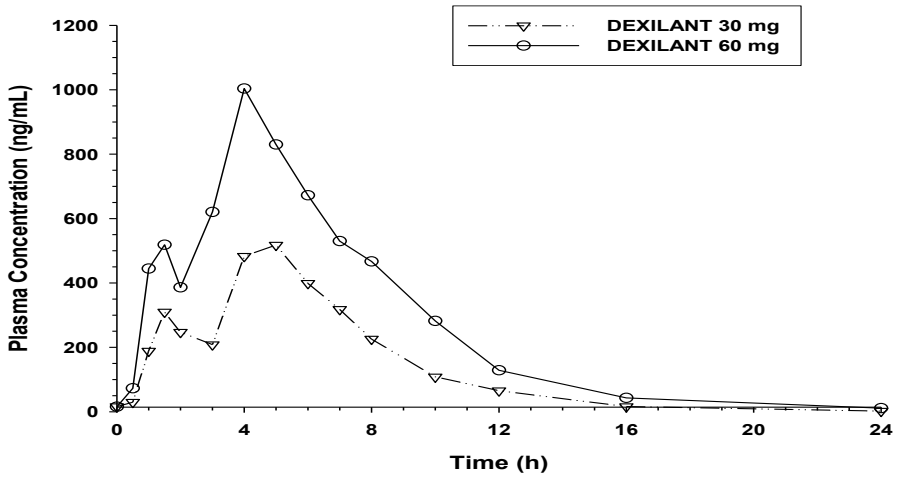
**Figure 1 - Mean Plasma Dexlansoprazole Concentration – Time Profile Following Oral Administration of 60 mg DEXILANT or 30 mg Lansoprazole Once Daily for 5 Days in Healthy Adult Subjects**




**Absorption:**

After oral administration of DEXILANT 30 mg or 60 mg to healthy subjects, mean $C_{max}$ and AUC values of dexlansoprazole increased approximately dose proportionally (see Figure 2).

**Figure 2 - Mean Plasma Dexlansoprazole Concentration – Time Profile Following Oral Administration of DEXILANT on Day 5 in Healthy Adult Subjects**




**Distribution:**

Plasma protein binding of dexlansoprazole ranged from 96.1% to 98.8% 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 40.3 L.

**Metabolism:**

Dexlansoprazole is extensively metabolized in the liver by oxidation, reduction, and subsequent formation of sulfate, glucuronide and glutathione conjugates to inactive metabolites. Oxidative metabolites are formed by the cytochrome P450 (CYP) enzyme system including hydroxylation mainly by CYP2C19, and oxidation to the sulfone by CYP3A4.

CYP2C19 is a polymorphic liver enzyme which exhibits three phenotypes in the metabolism of CYP2C19 substrates; extensive metabolizers (*1/*1), intermediate metabolizers (*1/mutant) and poor metabolizers (mutant/mutant). Systemic exposure of dexlansoprazole is generally higher in intermediate and poor metabolizers. Dexlansoprazole is the major circulating component in plasma, regardless of CYP2C19 metabolizer status. In CYP2C19 intermediate and extensive metabolizers, the major plasma metabolites are 5-hydroxy dexlansoprazole and its glucuronide conjugate, while in CYP2C19 poor metabolizers dexlansoprazole sulfone is the major plasma metabolite.

**Elimination:**

Following the administration of DEXILANT, no unchanged dexlansoprazole is excreted in urine. Following the administration of [$^{14}$C]dexlansoprazole to 6 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 5-days of 30 or 60 mg once daily administration.

**Effect of Food:**

DEXILANT can be taken without regard to food or the timing of food. In food-effect studies in healthy subjects receiving DEXILANT, increases in $C_{max}$ ranged from 12% to 55% and increases in AUC ranged from 9% to 37% under various fed conditions compared to fasting. However, no relevant differences

with regard to intragastric pH were observed. An additional study showed that administration of 60 mg DEXILANT prior to consumption of breakfast, lunch, dinner or an evening snack did not have an effect on dexlansoprazole exposure, or a clinically relevant effect on 24-hour intragastric pH control.

**Special Populations and Conditions**

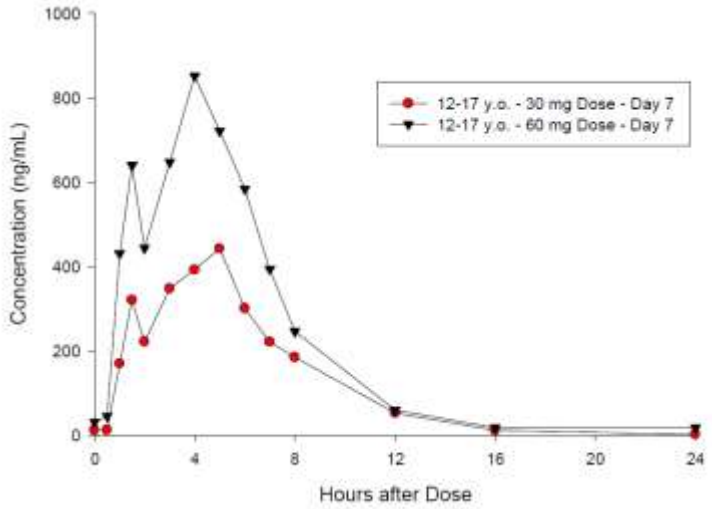
- **Pediatrics:** In a study of 36 adolescents 12 to 17 years old with symptomatic GERD, dexlansoprazole pharmacokinetics (See Figure 3 and Table 6) were similar to those observed in healthy adults (See Figure 2 and Table 5). In adolescents, dexlansoprazole mean $C_{max}$ was 81% to 105% of the adult mean $C_{max}$ value, mean AUC was 78% to 88% of the adult mean AUC value, and mean CL/F was 112% to 132% of the adult mean CL/F value.

**Table 6 - Mean (CV %) Pharmacokinetic Parameters in Adolescents 12 to 17 Years of Age with Symptomatic GERD on Day 7 After Administration of DEXILANT once daily for 7 days**

| Dose (mg) | $C_{max}$ (ng/mL) | $AUC_{\tau}$ (ng·h/mL) | CL/F (L/h) |
|---|---|---|---|
| 30 (N=17) | 691 (53%) | 2886 (47%) | 12.8 (48%) |
| 60 (N=18) | 1136 (51%) | 5120 (58%) | 15.3 (49%) |

*Note: area under the concentration-time curve during a dosing interval ($AUC_{\tau}$)*

**Figure 3 - Mean Dexlansoprazole Plasma Concentration – Time Profile Following Administration of 30 or 60 mg DEXILANT Capsules Once Daily for 7 Days in Adolescents 12 to 17 Years of Age with Symptomatic GERD**




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

- **Geriatrics:** In a study of 12 male and 12 female healthy subjects who received a single oral dose of DEXILANT 60 mg, the terminal elimination half-life of dexlansoprazole was statistically

significantly longer in geriatric subjects compared to younger subjects (2.23 and 1.5 hours, respectively). In addition, dexlansoprazole exhibited higher systemic exposure (AUC) in geriatric subjects (34.5% higher) than younger subjects. These differences were not clinically relevant. No dosage adjustment is necessary in geriatric patients. See 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS.

- **Sex:** In a study of 12 male and 12 female healthy subjects who received a single oral dose of DEXILANT 60 mg, females had higher systemic exposure (AUC) (42.8% higher) than males. No dosage adjustment is necessary in patients based on gender.
- **Hepatic Insufficiency:** In a study of 12 patients with moderately impaired hepatic function who received a single oral dose of DEXILANT 60 mg, plasma exposure (AUC) of bound and unbound dexlansoprazole in the hepatic impairment group was approximately 2 times greater compared to subjects with normal hepatic function. This difference in exposure was not due to a difference in protein binding between the two liver function groups. No adjustment for DEXILANT is necessary for patients with mild hepatic impairment (Child-Pugh Class A). DEXILANT 30 mg should be considered for patients with moderate hepatic impairment (Child-Pugh Class B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C). See 7 WARNINGS AND PRECAUTIONS.
- **Renal Insufficiency:** 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 subjects with renal impairment. See 7 WARNINGS AND PRECAUTIONS.

## 11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15° to 30°C).

## 12 SPECIAL HANDLING INSTRUCTIONS

No special handling instructions are required for this product.

## PART II: SCIENTIFIC INFORMATION

## 13 PHARMACEUTICAL INFORMATION

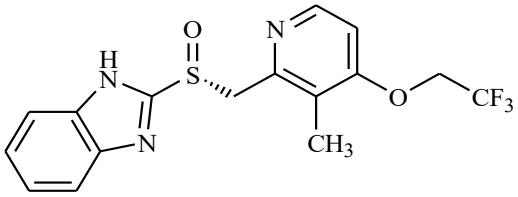
**Drug Substance**

Proper name: Dexlansoprazole

Chemical name: (+)-2-[(*R*)-{[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl] methyl} sulfinyl]-*1H*-benzimidazole

Molecular formula and molecular mass: $C_{16}H_{14}F_3N_3O_2S$, 369.36 g/mol

Structural formula:



Physicochemical properties: Dexlansoprazole is a white to nearly white crystalline powder which melts with decomposition at 140°C. Dexlansoprazole is the R-enantiomer of lansoprazole (a racemic mixture of the R- and S-enantiomers).

Dexlansoprazole is freely soluble in dimethylformamide, methanol, dichloromethane, ethanol, and ethyl acetate; soluble in acetonitrile; slightly soluble in ether; 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.

## 14 CLINICAL TRIALS

### 14.1 Clinical Trials by Indication

**Healing of Erosive Esophagitis in Adult Patients**

**Table 7 - Summary of patient demographics for adult clinical trials in healing of erosive esophagitis**

| Study # | Study design | Dosage, route of administration and duration | Study subjects (n) | Mean age (Range) | Sex |
|---|---|---|---|---|---|
| T-EE04-084 | Randomized, double-blind, active-controlled | DEXILANT: 60 mg QD, 90 mg QD, Oral<br>Lansoprazole delayed release: 30 mg QD, Oral<br>4 or 8 weeks | 2038 | 47.5 (18 to 87 years) | Males and females |
| T-EE04-085 | Randomized, double-blind, active-controlled | DEXILANT: 60 mg QD, 90 mg QD, Oral<br>Lansoprazole delayed release: 30 mg QD, Oral<br>4 or 8 weeks | 2054 | 47.9 (18 to 90 years) | Males and females |

*Trial Design and Study Demographics*: Two multi-center, double-blind, active-controlled, randomized, 8-week studies were conducted in patients with endoscopically confirmed erosive esophagitis (Table 7). 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 daily, DEXILANT 90 mg daily or lansoprazole 30 mg daily. 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 Grades A and B erosive esophagitis (mild) and 29% of patients had Grades C and D erosive esophagitis (moderate to severe) before treatment.

*Study Results:* By the life-table method of analysis DEXILANT 60 mg healed 92.3% to 93.1% of patients versus 86.1% to 91.5% for lansoprazole 30 mg after 8 weeks of treatment. Non-inferiority was demonstrated in both studies. Statistical superiority was not established using log-rank tests.

The crude rate estimates considered patients who did not have endoscopically documented healed erosive esophagitis and who discontinued prematurely as not healed. Based on crude rate estimates, healing rates at Week 4 (secondary) or Week 8 (primary) were higher for DEXILANT than lansoprazole (Table 8). Treatment with DEXILANT 60 mg was non-inferior to lansoprazole 30 mg at Week 8 in both studies. Statistical superiority of DEXILANT 60 mg over lansoprazole 30 mg was established in the first study but was not replicated in the second study.

**Table 8 - Erosive Esophagitis Healing Rates in Adults – All Grades**

| Study | Number of Patients (N) | Treatment Group (Daily) | Week 4 % Healed | Week 8 % Healed [a] | (95% CI) for the Treatment Difference (DEXILANT – Lansoprazole) at Week 8 | p-value Week 8 |
|---|---|---|---|---|---|---|
| 1 | 639 | DEXILANT 60 mg | 66.2 | 85.3 | (2.17, 10.48) [b] | 0.004* |
| | 656 | Lansoprazole 30 mg | 64.8 | 79.0 | | |
| 2 | 657 | DEXILANT 60 mg | 69.7 | 86.9 | (-1.45, 6.14) [b] | 0.234 |
| | 648 | Lansoprazole 30 mg | 65.4 | 84.6 | | |

CI = Confidence interval
[a] Primary efficacy endpoint by the crude rate method of analysis
[b] Demonstrated non-inferiority to lansoprazole
*Statistically significant

The life-table healing rates at Week 8 for patients with moderate to severe erosive esophagitis were 88.9% and 74.5% for DEXILANT 60 mg and lansoprazole 30 mg, respectively, in the first study. The difference was statistically significant (p=0.011). In the second study, the Week 8 life-table healing rates were 87.6% and 87.7% for DEXILANT 60 mg and lansoprazole 30 mg, respectively, and were not statistically significantly different.

The crude healing rates at Week 8 for patients with moderate to severe erosive esophagitis are presented in Table 9.

**Table 9 - Healing Rates at Week 8 – Moderate to Severe Erosive Esophagitis in Adults**

| Study | Number of Patients (N) | Treatment Group (Daily) | Week 8 % Healed [a] | p-value Week 8 |
|---|---|---|---|---|
| 1 | 182 | DEXILANT 60 mg | 79.7 | 0.002* |
| | 200 | Lansoprazole 30 mg | 65.0 | |
| 2 | 194 | DEXILANT 60 mg | 77.8 | 0.768 |
| | 190 | Lansoprazole 30 mg | 78.9 | |

[a] Healing rates are by the crude rate method of analysis
*Statistically significant

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

**Maintenance of Healed Erosive Esophagitis in Adult Patients**

**Table 10 - Summary of patient demographics for adult clinical trials in maintenance of healed erosive esophagitis**

| Study # | Study design | Dosage, route of administration and duration | Study subjects (n) | Mean age (Range) | Sex |
|---|---|---|---|---|---|
| T-EE05-135 | Randomized, double-blind, placebo-controlled | DEXILANT: 30 mg QD, 60 mg QD, Oral<br>Placebo QD, Oral<br>6 months | 445 | 49 (18 to 85) years | Males and females |

*Trial Design and Study Demographics*: A multi-center, double-blind, placebo-controlled, randomized study was conducted in patients who successfully completed a erosive esophagitis study and showed endoscopically confirmed healed erosive esophagitis (Table 10). Maintenance of healing and symptom relief over a six-month period were evaluated with DEXILANT 30 mg or 60 mg 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.

*Study Results:* By the life-table method, DEXILANT 30 mg and 60 mg demonstrated statistically significantly higher rates of maintenance of healed erosive esophagitis (74.9% and 82.5%, respectively) than placebo (27.2%) at Month 6 ($p<0.00001$).

Based on crude rate estimates, 66.4% percent of patients treated with 30 mg or 60 mg of DEXILANT remained healed over the six-month time period versus 14.3% of placebo patients ($p<0.00001$) (Table 11).

**Table 11 - Maintenance Rates a of Healed EE in Adults at Month 6**

| Number of Patients (N) [b] | Treatment Group (Daily) | Maintenance Rate |
|---|---|---|
| 125 | DEXILANT 30 mg | 66.4* |
| 119 | Placebo | 14.3 |

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

[b] Patients with at least one post baseline endoscopy

* Statistically significant vs. placebo

For patients with more severe grades of erosive esophagitis (Grades C or D) before healing, DEXILANT 30 mg and 60 mg also achieved statistically significantly higher 6-month maintenance rates than placebo by the life-table method. For the crude rate analysis, the trends in the results were similar to the life-table analysis.

DEXILANT 30 mg and 60 mg achieved statistically significantly ($p<0.00001$) greater percentages of 24-hour heartburn-free periods, and heartburn free nights during the study treatment period, compared to placebo (see Tables 12 and 13).

**Table 12 - Median Percentage of 24-Hour Heartburn-Free Periods of the Maintenance of Healed EE Study in Adults**

| Treatment Group (daily) | N | Heartburn-Free 24-hour Periods (Median %) |
|---|---|---|
| DEXILANT 30 mg | 132 | 96.1* |
| DEXILANT 60 mg | 147 | 90.9* |
| Placebo | 141 | 28.6 |

* Statistically significant vs. placebo (p<0.00001)

**Table 13 - Median Percentage of Nighttime Heartburn-Free Periods of the Maintenance of Healed EE Study in Adults**

| Treatment Group (daily) | N | Heartburn-Free Nights (Median %) |
|---|---|---|
| DEXILANT 30 mg | 132 | 98.9* |
| DEXILANT 60 mg | 147 | 96.2* |
| Placebo | 140 | 71.7 |

* Statistically significant vs. placebo (p<0.00001)

In a second study (N=451) of DEXILANT 60 mg and 90 mg versus placebo, DEXILANT 60 mg showed similar results to the first study in the maintenance of healed erosive esophagitis and heartburn relief. DEXILANT 90 mg did not provide additional clinical benefit over DEXILANT 60 mg.

**Symptomatic GERD in Adult Patients**

**Table 14 - Summary of patient demographics for adult clinical trials in symptomatic non-erosive GERD**

| Study # | Study design | Dosage, route of administration and duration | Study subjects (n) | Mean age (Range) | Sex |
|---|---|---|---|---|---|
| T-GD05-137 | Randomized, double-blind, multicenter, placebo-controlled, parallel-group, 3 arm | DEXILANT: 30 mg QD, 60 mg QD, Oral<br>Placebo QD, Oral<br>4 weeks | 947 | 48 (18 to 86) years | Males and females |

*Trial Design and Study Demographics*: A multi-center, double-blind, placebo-controlled, randomized, 4-week study was conducted in patients with a diagnosis of symptomatic GERD made primarily by presentation of symptoms (Table 14). These patients who identified heartburn as their primary symptom, had a history of heartburn for 6 months or longer, had heartburn on at least 4 of 7 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.

*Study Results*: DEXILANT 30 mg provided statistically significantly greater percent of days with heartburn-free 24-hour periods and percent of nights without heartburn over placebo as assessed by daily diary over 4 weeks (Table 15). DEXILANT 60 mg was studied and provided no additional clinical benefit over DEXILANT 30 mg.

**Table 15 - Median Percentages of Heartburn Relief During the 4 Week Treatment Period of the Symptomatic GERD Study in Adults**

| N | Treatment Group (daily) | Heartburn-Free 24-Hour Periods (%) | Nights without Heartburn (%) |
|---|---|---|---|
| 312 | DEXILANT 30 mg | 54.9* | 80.8* |
| 310 | Placebo | 18.5 | 51.7 |

* Statistically significant vs. placebo (p<0.00001)

A higher percentage of patients on DEXILANT 30 mg had heartburn-free 24-hour periods compared to placebo through 4 weeks of treatment.

**Healing of EE, Maintenance of Healed EE: Adolescents 12 to 17 Years of Age**

**Table 16 - Summary of patient demographics for adolescent clinical trials in healing of erosive esophagitis and maintenance of healed erosive esophagitis**

| Study # | Study design | Dosage, route of administration and duration | Study subjects (n) | Mean age (Range) | Sex |
|---|---|---|---|---|---|
| TAK-390MR_207 | Healing: open-label, multicenter, multiple-dose, noncomparative<br>Maintenance: randomized, double-blind, multicenter, multiple-dose, parallel-group, placebo-controlled | Healing (8 weeks):<br>DEXILANT 60 mg QD, Oral<br>Maintenance (16 weeks):<br>DEXILANT 30 mg QD, Oral<br>Placebo QD, Oral | Healing:<br>62<br>Maintenance:<br>51 | 15 (12 to 17) years | Males and females |

*Trial Design and Study Demographics*: In a multi-center, 24-week study, 62 adolescents 12 to 17 years of age with a documented history of GERD for at least 3 months and endoscopically-proven EE were treated with dexlansoprazole 60 mg capsule once daily, for 8 weeks (single-arm open-label healing phase), followed by a 16-week maintenance phase (randomized double-blind placebo-controlled) (Table 16). The median age was 15 years with males accounting for 61% of the patients. Based on the

Los Angeles Classification Grading Scale, 96.8% of the EE patients had mild EE (Grades A and B), and 3.2% of patients had moderate to severe EE (Grades C and D) before treatment.

*Study Results*: Among the 62 patients enrolled in the healing phase, 58 patients completed the 8-week treatment, with 51 (82.3% out of 62) patients achieving EE healing by week 8. This corresponds to 87.9% of the 58 patients who completed the 8-week treatment.

After the initial 8 weeks of treatment, 51 patients with endoscopically confirmed healed EE were randomized to receive dexlansoprazole 30 mg capsule or placebo once daily for an additional 16 weeks, in order to assess the maintenance of EE healing. A total of 38 patients completed the maintenance phase. Eighty-two percent (81.8%) of patients treated with dexlansoprazole 30 mg capsule remained healed over the four-month treatment period as confirmed by endoscopy. The rate was 58.3% in patients treated with placebo (see Table 17).

**Table 17 - Maintenance of Healed EE After 16 weeks in Adolescents 12 to 17 Years of Age**

| N | Treatment Group (daily) | Maintenance Rate (%) |
|---|---|---|
| 22 | DEXILANT 30 mg | 81.8 |
| 24 | Placebo | 58.3 |

During the 16-week maintenance period, median percentage of 24-hour heartburn-free periods were 86.6% for those receiving dexlansoprazole 30 mg capsule compared to 68.1% for those receiving placebo.

**Symptomatic Non-Erosive GERD: Adolescents 12 to 17 Years of Age**

**Table 18 - Summary of patient demographics for adolescent clinical trials in symptomatic non-erosive GERD**

| Study # | Study design | Dosage, route of administration and duration | Study subjects (n) | Mean age (Range) | Sex |
|---|---|---|---|---|---|
| TAK-390MR_206 | Open-label, multicenter, multiple-dose, noncomparative | DEXILANT: 60 mg QD, Oral<br>4 weeks | 104 | 15 (12 to 17) years | Males and females |

*Trial Design and Study Demographics*: In a single-arm uncontrolled, open-label, multi-center study, 104 adolescents 12 to 17 years of age with symptomatic non-erosive GERD were treated with dexlansoprazole 30 mg capsule once daily, for 4 weeks (Table 18). Patients had a documented history of GERD symptoms for at least 3 months prior to screening, reported heartburn on at least three out of seven days during screening, and no esophageal erosions as confirmed by endoscopy. Patients ranged in age from 12 to 17 years (median age 15 years) with females accounting for 70% of the patients.

*Study Results:* During the 4-week treatment period, the median percentage of 24-hour heartburn free periods was 47.3%.

Overall, the efficacy results for healing of EE, maintenance of healed EE, and symptomatic non-erosive GERD in adolescents 12 to 17 years of age as enrolled in the studies did not appear to be substantially different from those reported in adults.

## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

**General Toxicology:** *Multi-dose Studies:* A thirteen-week oral toxicity study was conducted in Wistar rats. Animals were administered 5, 15 or 50 mg/kg/day of dexlansoprazole or 50 mg/kg/day of lansoprazole. Pharmacologically related increases in stomach weight were observed for all doses of dexlansoprazole and lansoprazole. The only histological findings attributed to test article treatment were eosinophilia of chief cells in the stomach at 15 and 50 mg/kg/day of dexlansoprazole and 50 mg/kg/day of lansoprazole, and slight centrilobular hepatocyte hypertrophy in the liver at 50 mg/kg/day of dexlansoprazole and lansoprazole.

In a thirteen-week oral toxicity study in dogs, animals were administered 5, 15 or 50 mg/kg/day of dexlansoprazole or 50 mg/kg/day of lansoprazole. Systemic exposure to dexlansoprazole generally was higher in animals dosed with dexlansoprazole at 50 mg/kg/day than with the same dosage of lansoprazole. The effects of dexlansoprazole and lansoprazole administered at 50 mg/kg/day were essentially the same. Pharmacologically related increases in stomach weight were observed at 15 and 50 mg/kg/day dexlansoprazole and lansoprazole 50 mg/kg/day. The only histological findings attributed to test article treatment were parietal cell vacuolation and/or single cell necrosis and slight accumulation of bile in hepatocellular canaliculi.

The no-observed-adverse-effect-level (NOAEL) of dexlansoprazole was 15 mg/kg/day in rats and 5 mg/kg/day in dogs.

**Carcinogenicity:** Lansoprazole is a racemic mixture of R- and S-enantiomers. Following administration of lansoprazole in humans and animals, the major component circulating in plasma is dexlansoprazole, the R-enantiomer of lansoprazole. Therefore, the carcinogenic potential of dexlansoprazole was assessed using existing 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 ($mg/m^2$) basis of a 50 kg person of average height (1.46 $m^2$ BSA) given the recommended human dose of lansoprazole of 30 mg/day (22.2 $mg/m^2$). Lansoprazole produced dose-related gastric ECL cell hyperplasia and ECL cell carcinoids in both male and female rats. See 10.2 Pharmacodynamics.

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 lansoprazole human dose based on BSA) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg lansoprazole/kg/day (13 times the recommended lansoprazole human dose based on BSA) in a 1-year toxicity study.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with lansoprazole doses of 15 mg to 600 mg/kg/day, 2 to 80 times the recommended human dose based on BSA. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. Lansoprazole also induced a low, non-dose-related incidence of carcinoid tumors in the gastric mucosa in several dose groups (one female mouse in the 15 mg/kg/day group, one male mouse in the 150 mg/kg/day group, and 2 males and 1 female in the 300 mg/kg/day group). It also produced an increased incidence of liver tumors

(hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 mg and 600 mg lansoprazole/kg/day (40 to 80 times the recommended lansoprazole human dose based on BSA) and female mice treated with 150 mg to 600 mg lansoprazole/kg/day (20 to 80 times the recommended human 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 lansoprazole human dose based on BSA).

**Genotoxicity:** Dexlansoprazole was positive in the Ames test. In an *in vitro* chromosome aberration test using Chinese hamster lung cells, dexlansoprazole was judged positive (equivocal) because the percentage of affected cells increased slightly but did not reach the pre-set criteria for a positive response. Dexlansoprazole was negative in the *in vivo* mouse micronucleus test.

**Reproductive and Developmental Toxicology:** An embryo-fetal toxicity study conducted in pregnant rabbits at oral dexlansoprazole doses up to 30 mg/kg/day (approximately 9-fold the maximum recommended human dexlansoprazole dose [60 mg] based on BSA) showed that exposure increased with dosage, and there were no substantive differences in the toxic effects of dexlansoprazole and lansoprazole. Dams treated with both test articles experienced transient effects on food consumption, body weights and fecal volume. No adverse effects on reproductive parameters nor test article-related fetal abnormalities occurred with either test article. The incidence of unossified talus was increased at 30 mg/kg/day of dexlansoprazole and lansoprazole. The dexlansoprazole NOAEL for general toxicity in the dams was 3 mg/ kg/day. For reproductive toxicity, the NOAEL was greater than or equal to 30 mg/kg/day. For embryo-fetal development, the NOAEL was 10 mg/kg.

Reproduction studies performed in pregnant rats with oral lansoprazole at doses up to 150 mg/kg/day (40 times the recommended human dose based on BSA) and in pregnant rabbits at oral lansoprazole doses up to 30 mg/kg/day (16 times the recommended human dose based on BSA) revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

**Juvenile Animal Toxicity Data:** In a juvenile rat study, adverse effects on bone growth and development and heart valves were observed at lansoprazole doses higher than the maximum recommended equivalent human dose.

An eight-week oral toxicity study with a four-week recovery phase was conducted in juvenile rats with lansoprazole administered from postnatal Day 7 (age equivalent to neonatal humans) through 62 (age equivalent to approximately 14 years in humans) at doses of 40 to 500 mg/kg/day.

Heart valve thickening occurred at a lansoprazole dose of 500 mg/kg/day (approximately three to five times the expected dexlansoprazole exposure based on AUC in pediatric patients less than 12 years of age). Heart valve thickening was not observed at the next lower dose (250 mg/kg/day) and below. The findings trended towards reversibility after a four-week drug-free recovery period.

No effects on heart valves were observed in a 13-week intravenous toxicity study of lansoprazole in adolescent rats (approximately 12 years human age equivalence) at systemic exposures similar to those achieved in the eight-week oral toxicity study in juvenile (neonatal) rats.

In the eight-week oral toxicity study of lansoprazole, doses equal to or greater than 100 mg/kg/day produced delayed growth, with impairment of weight gain observed as early as postnatal Day 10 (age equivalent to neonatal humans). At the end of treatment, the signs of impaired growth at 100 mg/kg/day and higher included reductions in body weight (14% to 44% compared to controls), absolute weight of multiple organs, femur weight, femur length and crown-rump length. Femoral growth plate thickness was reduced only in males and only at the 500 mg/kg/day dose. The effects related to

delayed growth persisted through the end of the 4-week recovery period. Longer term data were not collected.

In a follow-up developmental toxicity study, juvenile rats (12 rats per dose group) were orally administered with 250 and/or 500 mg/kg/day lansoprazole for four or eight weeks starting on postnatal Day (PND) 7 (age equivalent to neonatal humans), PND 14 (age equivalent to approximately one year in humans), or PND 21 (age equivalent to approximately two years in humans).

Signs of toxicity (lower mean body weight gain and heart valve thickening) were observed in almost all dose groups of juvenile rats. Incidences of heart valve thickening were 2/12, 5/12 and 0/12, respectively, in juvenile rats dosed starting at ages 7, 14, and 21 day with 500 mg/kg/day lansoprazole for 4 weeks. Heart valve thickening in animals dosed with 500 mg/kg/days lansoprazole for eight weeks starting at PND 7, 14, and 21 were 2/12, 7/12, and 1/12, respectively.

Due to high incidence of mortality (9 of 24 males were found dead and 12 of 24 males were euthanized between PND 18 and PND 21) in the 500 mg/kg/day dose group starting at PND 14, dose level for this group was changed from 500 mg/kg/day to 250 mg/kg/day. Incidences of heart valve thickening in juvenile rats dosed with 250 mg/kg/day (approximately two times the expected dexlansoprazole exposure based on AUC in pediatric patients less than 12 years of age) starting at PND 14 were two (2/12) and one (1/11) for four weeks and eight weeks exposures, respectively. Incidences of the heart valve thickening were observed in almost all dose groups. Juvenile rats younger than PND 21 (age equivalent to approximately two years in humans) were more sensitive to the development of heart valve thickening.

The relevance of heart valve thickening in these studies to pediatric patients less than 12 years of age is unknown. These findings are not relevant for patients 12 years of age and older.

## PATIENT MEDICATION INFORMATION

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**[Pr]DEXILANT®**

**(dexlansoprazole) delayed release capsules**

Read this carefully before you start taking **DEXILANT** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **DEXILANT**.

### What is DEXILANT used for?

DEXILANT is used in people 12 years of age and older to:

- help heal the throat:
  - damaged by acid backing up from the stomach to the throat (erosive reflux esophagitis).
  - help maintain the healed throat.
- relieve symptoms of non-erosive gastroesophageal reflux disease (GERD) such as:
  - heartburn during the day and night.
  - the burning, burping and sour taste.

### How does DEXILANT work?

DEXILANT is a medicine called a proton pump inhibitor (PPI). PPIs reduce the amount of acid your stomach makes.

DEXILANT capsules contain two different types of granules, tiny dissolving beads that release medicine. The first granule begins releasing medicine within 1 hour. The rest of the medicine is released 4-5 hours later, so the medicine continues to work later in the day.

### What are the ingredients in DEXILANT?

Medicinal ingredients: dexlansoprazole.

Non-medicinal ingredients:

Capsule granules: colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose 2910, low-substituted hydroxypropyl cellulose, magnesium carbonate, methacrylic acid copolymer, polyethylene glycol 8000, polysorbate 80, sucrose, sugar spheres, talc, titanium dioxide, and triethyl citrate.

Capsule shell: carrageenan, hypromellose, and potassium chloride.

Capsule shell color: blue contains FD&C Blue No.2 aluminum lake; gray contains black ferric oxide; and both contain titanium dioxide.

### DEXILANT comes in the following dosage forms:

- Capsules, 30 mg or 60 mg.

**Do not use DEXILANT if:**

- you are allergic to DEXILANT or any of its ingredients. (See **What are the ingredients in DEXILANT?**).
- you are currently taking a medication called rilpivirine.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take DEXILANT. Talk about any health conditions or problems you may have, including if you:**

- are taking other medications. (See **The following may interact with DEXILANT**).
- have liver problems.
- are pregnant or planning to become pregnant.
- are breastfeeding or planning to breastfeed.
- have signs of low magnesium in the body (hypomagnesemia) with symptoms such as:
    - rapid or irregular heartbeat (palpitations).
    - brain symptoms such as dizziness, seizures.
    - muscle symptoms such as twitching, cramps, spasms (tetany).
- are due to have a specific blood test (Chromogranin A).

**Other warnings you should know about:**

Tell your doctor if you experience the following symptoms before taking DEXILANT:

- unexplained weight loss.
- severe or persistent diarrhea.
- repeated vomiting.
- vomiting blood.
- dark stools.
- tiredness (anemia).
- difficulty in swallowing.

DEXILANT may help your acid-related symptoms. However, you could still have serious stomach problems. Talk to your doctor if your symptoms continue.

You should take DEXILANT exactly as prescribed. You will use the lowest dose and shortest time suitable for your condition. Talk to your doctor if you have any concerns about your treatment.

Depending on your condition, your doctor may tell you to use this type of medicine (proton pump inhibitors) for a longer period.

Using proton pump inhibitors for a long time (every day for a year or longer) may increase risks of broken bones of the hip, wrist or spine. Talk to your doctor about this risk.

Long term use of proton pump inhibitors may interfere with the absorption of Vitamin B12 from the diet. This may cause a shortage of Vitamin B12 in your body. Talk to your doctor.

Using DEXILANT for a long period of time may cause a growth in your stomach (polyp), especially after one year.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with DEXILANT:**

- ampicillin.
- atazanavir.
- digoxin.
- iron salts.
- ketoconazole.
- methotrexate.
- nelfinavir.
- saquinavir/ritonavir.
- sucralfate.
- tacrolimus.
- theophylline.
- warfarin.

**How to take DEXILANT:**

- Do not crush or chew capsules or granules.
- Take DEXILANT at any time of day, with or without food. By either:
  - Swallowing capsule whole, with water.
  - Or, if you have trouble swallowing capsules, the capsules can be opened and taken with applesauce or water, as follows:

  Applesauce:

  DEXILANT capsules can be opened and the contents sprinkled on a tablespoon of applesauce. Swallow immediately. Granules should not be chewed.

  Water with an Oral Syringe:

  1. Open the capsule and empty the granules into a clean container with 20 mL of water.
  2. Draw up the water and granules mixture into an oral syringe.
  3. Swirl the syringe gently, and give the mixture into the mouth right away. Do not save the water and granule mixture for later use.
  4. Refill the syringe with 10 mL of water, and swirl gently. Give the water into the mouth.
  5. Repeat step 4.

  Water through a Nasogastric Tube: If you have a nasogastric tube (size 16 French or larger)

  1. Open the capsule and empty the granules into a clean container with 20 mL of water.
  2. Draw up the water and granules mixture into a catheter-tip syringe.
  3. Swirl the syringe gently and connect the syringe to the nasogastric tube. Right away, give the mixture through the nasogastric tube into the stomach. Do not save the water and granule mixture for later use.
  4. Refill the syringe with 10 mL of water, swirl gently, and flush the nasogastric tube with water.
  5. Repeat step 4.

**Usual dose:**

The recommended dose is not the same for all conditions. Your doctor will have told you what dose to take for your condition. Follow your doctor's directions carefully.

| Condition | Adult or Adolescent Dose | How Often | For How Long |
|---|---|---|---|
| Healing of erosive esophagitis. | 60 mg. | Once daily. | Up to 8 weeks. |

| | | | |
|---|---|---|---|
| Maintaining healed erosive esophagitis. | 30 to 60 mg. | Once daily. | Adults: Up to 6 months.<br>Adolescents aged 12 to 17: Up to 4 months. |
| Symptoms of non-erosive GERD. | 30 mg. | Once daily. | 4 weeks. |

**Overdose:**

If you think you, or a person you are caring for, have taken too much DEXILANT, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

**Missed Dose:**

If you miss a dose, take it as soon as you remember. If it is almost time for the next dose, skip the missed dose. Take the next dose at your regular time. Do not double doses.

**What are possible side effects from using DEXILANT?**

Like all medications, DEXILANT can cause side effects. Serious side effects are uncommon. These are not all the possible side effects you may feel when taking DEXILANT. If you experience any side effects not listed here, tell your healthcare professional.

The most common side effects are:

- constipation.
- diarrhea.
- gas.
- headache.
- nausea.
- stomach pain.

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

- New or worsening joint pain.
- Rash on your cheeks or arms that gets worse in the sun.

Your symptoms may get worse after stopping your medication. This may occur as your stomach may increase the production of acid.

| **Serious side effects and what to do about them** | | | |
|---|---|---|---|
| **Symptom / effect** | **Talk to your healthcare professional** | | **Stop taking drug and get immediate medical help** |
| | **Only if severe** | **In all cases** | |
| **RARE** | | | |
| *Clostridium difficile* colitis (Bowel inflammation): Symptoms include severe (watery or bloody) diarrhea, fever, abdominal pain or tenderness. | | | ✓ |

| Serious side effects and what to do about them | | | |
|---|---|---|---|
| **Symptom / effect** | **Talk to your healthcare professional** | | **Stop taking drug and get immediate medical help** |
| | **Only if severe** | **In all cases** | |
| *Clostridium difficile* colitis (Bowel inflammation): If you are currently taking or have recently taken antibiotics and you develop diarrhea, contact your doctor, even if the diarrhea is relatively mild. | | ✓ | |
| Convulsion or seizure. | | | ✓ |
| Liver problems (hepatitis or cholestasis): Symptoms include dark-coloured urine and pale stools, yellow tinge to skin and eyes (jaundice), stomach pain. | | ✓ | |
| Microscopic colitis (inflammation of the gut): symptoms include chronic watery diarrhea, abdominal pain, cramps or bloating, weight loss, nausea, uncontrollable bowel movement, signs of dehydration such as: extreme thirst, less frequent urination, dark-coloured urine, fatigue, dizziness, confusion.<br>The symptoms of microscopic colitis can come and go frequently. If you have watery diarrhea that lasts more than a few days, contact your doctor. | ✓ | | |
| Severe Cutaneous Adverse Reactions (SCAR) (Severe Skin Reactions): Skin rash which may have blistering, peeling or bleeding on any part of your skin (including your lips, eyes, mouth, nose, genitals, hands or feet). You may also experience fever, chills, body aches, shortness of breath, or enlarged lymph nodes. | | | ✓ |
| Serious skin reactions: Symptoms include widespread rash, itching, or hives. Peeling of the skin, blisters on the skin, mouth, nose, eyes and genitals are other symptoms. | | | ✓ |
| **UNKNOWN** | | | |
| Tubulointerstitial nephritis (kidney problems): decreases in urination, blood in your urine. | | ✓ | |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to

interfere with your daily activities, tell your healthcare professional.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

Store DEXILANT at room temperature, 15°- 30°C.

Keep out of reach and sight of children.

**If you want more information about DEXILANT:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.takeda.com/en-ca, or by calling 1-800-268-2772.

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