

PRESCRIBING INFORMATION

1 NAME OF THE MEDICINAL PRODUCT

DEXILANT (dexlansoprazole) modified-release capsules, for oral use. DEXILANT is available as capsules in 30 mg and 60 mg strengths.

2 THERAPEUTIC INDICATIONS

Dexilant 30 mg is indicated in adults and in adolescents aged 12 to 17 years for the following:

- Maintenance of healed erosive reflux oesophagitis and maintenance of relief of heartburn
- Short-term treatment of heartburn and acid regurgitation associated with symptomatic non-erosive gastro-oesophageal reflux disease (GORD).

Dexilant 60 mg is indicated in adults and in adolescents aged 12 to 17 years for the following:

- Treatment of erosive reflux oesophagitis

3 DOSAGE AND ADMINISTRATION

3.1 Recommended Dosage in Adults and adolescents aged 12 to 17 years

DEXILANT is available as capsules in 30 mg and 60 mg strengths for adult and adolescents aged 12 to 17 years use. Directions for use in each indication are summarized in Table 1.

Table 1. Recommended DEXILANT Capsules dosage regimen by indication in Adults and adolescents aged 12 to 17 years

Indication	Dosage of DEXILANT Capsules	Duration
Treatment of erosive reflux oesophagitis	One 60 mg capsule once daily	Up to 8 weeks
Maintenance of healed erosive reflux oesophagitis and maintenance of relief of heartburn	One 30 mg capsule once daily	Controlled studies did not extend beyond 6 months in adults and 16 weeks in patients 12 to 17 years of age
Symptomatic non-erosive	One 30 mg capsule once daily	4 weeks

gastro- oesophageal reflux disease (GORD)		
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3.2 Dosage Adjustment in Patients with Hepatic Impairment

For the treatment of erosive reflux oesophagitis

For patients with moderate hepatic impairment (Child-Pugh Class B), the recommended dosage is 30 mg DEXILANT once daily for up to eight weeks. DEXILANT is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) [*see Use in Specific Populations (9.5)*].

3.3 Important Administration Information

- Take without regard to food.
- 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.
- 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.

4 DOSAGE FORMS AND STRENGTHS

DEXILANT modified-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”.

5 CONTRAINDICATIONS

- DEXILANT is contraindicated in patients with known hypersensitivity to any component of the formulation [see Description (11)]. Hypersensitivity reactions, may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute tubulointerstitial nephritis and urticaria [see Warning and Precautions (6.2), Adverse Reactions (7)]
- PPIs, including DEXILANT, are contraindicated with rilpivirine-containing products [see Drug Interactions (8)].

6 WARNINGS AND PRECAUTIONS

6.1 Presence of Gastric Malignancy

In adults, symptomatic response to therapy with DEXILANT does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing in adult patients who have a suboptimal response or an early symptomatic relapse after completing treatment with a PPI. In older patients, also consider an endoscopy.

6.2 Acute Tubulointerstitial Nephritis

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking PPIs and may occur at any point during PPI therapy. Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function (e.g., malaise, nausea, anorexia). In reported case series, some patients were diagnosed on biopsy and in the absence of extra-renal manifestations (e.g., fever, rash or arthralgia).

Discontinue DEXILANT and evaluate patients with suspected acute TIN [see Contraindications (5)].

6.3 *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 (7.2)].

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

6.4 Bone Fracture

Several published observational studies suggest that PPI therapy may be associated

with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the conditions being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines [*see Dosage and Administration (3), Adverse Reactions (7.2)*].

6.5 Severe cutaneous adverse reactions

Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with the use of PPIs [*see Adverse Reactions (7.2)*]. Discontinue DEXILANT at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

6.6 Cutaneous and Systemic Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE.

The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.

Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving DEXILANT, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in four to 12 weeks. Serological testing (e.g., ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

6.7 Cyanocobalamin (Vitamin B12) Deficiency

Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than three years) may lead to malabsorption of cyanocobalamin (Vitamin B12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed in patients treated with DEXILANT.

6.8 Hypomagnesemia and Mineral Metabolism

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 and may exacerbate underlying hypocalcemia in at-risk patients. 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 (7.2)*].

Consider monitoring magnesium and calcium levels prior to initiation of DEXILANT and periodically while on treatment in patients with a preexisting risk of hypocalcemia (e.g., hypoparathyroidism). Supplement with magnesium and/or calcium as necessary. If hypocalcemia is refractory to treatment, consider discontinuing the PPI.

6.9 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 (8), Clinical Pharmacology (12.2)*].

6.10 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 (8)*].

6.11 Fundic Gland Polyps

PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPI users who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

7 ADVERSE REACTIONS

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

- Acute Tubulointerstitial Nephritis [*see Warnings and Precautions (6.2)*]
- *Clostridium difficile* - Associated Diarrhea [*see Warnings and Precautions (6.3)*]
- Bone Fracture [*see Warnings and Precautions (6.4)*]
 - Severe Cutaneous Adverse Reactions [*see Warnings and Precautions (6.5)*]
- Cutaneous and Systemic Lupus Erythematosus [*see Warnings and Precautions (6.6)*]

- Cyanocobalamin (Vitamin B-12) Deficiency [see *Warnings and Precautions (6.7)*]
- Hypomagnesemia and Mineral Metabolism [see *Warnings and Precautions (6.8)*]
- Fundic Gland Polyps [see *Warnings and Precautions (6.11)*]

7.1 Clinical Trials Experience

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

Adults

The safety of DEXILANT was evaluated in 4548 adult patients in controlled and single-arm clinical trials, including 863 patients treated for at least six months and 203 patients treated for one year. Patients ranged in age from 18 to 90 years (median age 48 years), with 54% female, 85% Caucasian, 8% Black, 4% Asian, and 3% Other races. Six randomized controlled clinical trials were conducted for the treatment of erosive reflux oesophagitis, maintenance of healed erosive reflux oesophagitis, and symptomatic GORD, which included 896 patients on placebo, 455 patients on DEXILANT 30 mg, 2218 patients on DEXILANT 60 mg, 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 than placebo in the controlled studies are presented in *Table 2*.

Table 2. Common Adverse Reactions in Controlled Studies in Adults					
Adverse Reaction	Placebo (N=896) %	DEXILANT 30 mg (N=455) %	DEXILANT 60 mg (N=2218) %	DEXILANT 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 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, oesophagitis, gastric polyp, gastritis, gastroenteritis, gastrointestinal disorders, gastrointestinal hypermotility disorders, GORD, 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 single-arm trial 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.

Pediatrics

The safety of DEXILANT was evaluated in controlled and single-arm clinical trials including 166 pediatric patients, 12 to 17 years of age for the treatment of symptomatic non-erosive GORD, treatment of erosive reflux oesophagitis, maintenance of healed erosive reflux oesophagitis and maintenance of relief of heartburn [see *Clinical Studies (14.4)*].

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

Other Adverse Reactions

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

7.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use 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, fundic gland polyps

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), toxic epidermal necrolysis (TEN) (some fatal), DRESS, AGEP.

Infections and Infestations: Clostridium difficile associated diarrhea

Metabolism and Nutrition Disorders: hypomagnesemia, hypocalcemia, hypokalemia, 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

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<https://sideeffects.health.gov.il>

8 DRUG INTERACTIONS

Tables 3 and 4 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 3. Clinically Relevant Interactions Affecting Drugs Co-Administered with DEXILANT and Interactions with Diagnostics	
Antiretrovirals	
<i>Clinical Impact:</i>	<p>The effect of PPIs on antiretroviral drugs is variable. The clinical importance and the mechanisms behind these interactions are not always known.</p> <ul style="list-style-type: none"> • 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>	<p><u>Rilpivirine-containing products:</u> Concomitant use with DEXILANT is contraindicated [see <i>Contraindications (5)</i>]. See prescribing information.</p> <p><u>Atazanavir:</u> See prescribing information for atazanavir for dosing information.</p> <p><u>Nelfinavir:</u> Avoid concomitant use with DEXILANT. See prescribing information for nelfinavir.</p> <p><u>Saquinavir:</u> See the prescribing information for saquinavir and monitor for potential saquinavir toxicities.</p> <p><u>Other antiretrovirals:</u> See prescribing information.</p>
Warfarin	
<i>Clinical Impact:</i>	<p>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.</p>

<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 (6.10)</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 (6.9), Clinical Pharmacology (12.2)</i>].
<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 (12.2)</i>].
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 4. Clinically Relevant Interactions Affecting DEXILANT When Co-administered with Other Drugs and substances	
CYP2C19 or CYP3A4 Inducers	
<i>Clinical Impact:</i>	Decreased exposure of dexlansoprazole when used concomitantly with strong inducers [see <i>Clinical Pharmacology (12.3)</i>].
<i>Intervention:</i>	<u>St. John's Wort, rifampin</u> : Avoid concomitant use with 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 (12.3)</i>].
<i>Intervention:</i>	<u>Voriconazole</u> : See prescribing information.

9 USE IN SPECIFIC POPULATIONS

9.1 Pregnancy

Risk Summary

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

Dexlansoprazole is the R-enantiomer of lansoprazole, and published observational studies of lansoprazole use during pregnancy did not demonstrate an association of adverse pregnancy-related outcomes with lansoprazole (see Data).

In animal reproduction studies, oral administration of lansoprazole to rats during organogenesis through lactation at 1.8 times the maximum recommended human dexlansoprazole dose produced reductions in the offspring in femur weight, femur length, crown-rump length and growth plate thickness (males only) on postnatal Day 21 (*see Data*). These effects were associated with reduction in body weight gain. Advise pregnant women of the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

Dexlansoprazole is the R-enantiomer of lansoprazole. Available data from published observational studies failed to demonstrate an association of adverse pregnancy-related outcomes and lansoprazole use. Methodological limitations of these observational studies cannot definitely establish or exclude any drug-associated risk during pregnancy. In a prospective study by the European Network of Teratology Information Services, outcomes from a group of 62 pregnant women administered median daily doses of 30 mg of lansoprazole were compared to a control group of 868 pregnant women who did not take any PPIs. There was no difference in the rate of major malformations between women exposed to PPIs and the control group, corresponding to a Relative Risk (RR)=1.04, [95% Confidence Interval (CI) 0.25-4.21]. In a population-based retrospective cohort study covering all live births in Denmark from 1996 to 2008, there was no significant increase in major birth defects during analysis of first trimester exposure to lansoprazole in 794 live births. A meta-analysis that compared 1,530 pregnant women exposed to PPIs in at least the first trimester with 133,410 unexposed pregnant women showed no significant increases in risk for congenital malformations or spontaneous abortion with exposure to PPIs (for major malformations Odds Ratio (OR)=1.12, [95% CI 0.86-1.45] and for spontaneous abortions OR=1.29, [95% CI 0.84-1.97]).

Animal Data

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

body surface area) during organogenesis revealed no effects on fetuses due to lansoprazole.

A pre- and postnatal developmental toxicity study in rats with additional endpoints to evaluate bone development was performed with lansoprazole at oral doses of 10 to 100 mg/kg/day (0.2 to 1.8 times the maximum recommended human dexlansoprazole dose of 60 mg based on dexlansoprazole AUC [area under the plasma concentration-time curve]) administered during organogenesis through lactation. Maternal effects observed at 100 mg/kg/day (1.8 times the maximum recommended human dexlansoprazole dose of 60 mg based on dexlansoprazole AUC) included increased gestation period, decreased body weight gain during gestation, and decreased food consumption. The number of stillbirths was increased at this dose, which may have been secondary to maternal toxicity. Body weight of pups was reduced at 100 mg/kg/day starting on postnatal Day 11. Femur weight, femur length, and crown-rump length were reduced at 100 mg/kg/day on postnatal Day 21. Femur weight was still decreased in the 100 mg/kg/day group at age 17 to 18 weeks. Growth plate thickness was decreased in the 100 mg/kg/day males on postnatal Day 21, and was increased in the 30 and 100 mg/kg/day males at age 17 to 18 weeks. The effects on bone parameters were associated with reduction in body weight gain.

9.2 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. 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.

9.3 Pediatric Use

The use of DEXILANT is not recommended for the treatment of symptomatic non erosive GORD in pediatric patients one month to less than one year of age because lansoprazole (the racemic mixture) was not shown to be effective in a multicenter, double-blind controlled trial, and nonclinical studies with lansoprazole have demonstrated an adverse effect of heart valve thickening and bone changes.

The safety and effectiveness of DEXILANT have not been established in pediatric patients less than 12 years of age. DEXILANT is not recommended in pediatric patients less than 12 years of age. Nonclinical studies in juvenile rats with lansoprazole have demonstrated an adverse effect of heart valve thickening and bone changes at lansoprazole doses higher than the maximum recommended equivalent human dose, as described below in *Juvenile Animal Toxicity Data*.

The safety and effectiveness of DEXILANT have been established in pediatric patients 12 to 17 years of age for the healing of all grades of erosive reflux oesophagitis, the maintenance of healed erosive reflux oesophagitis and maintenance of relief of heartburn, and treatment of heartburn associated with symptomatic non-erosive GORD.

Use of DEXILANT in this age group is supported by evidence from adequate and well-controlled studies of DEXILANT in adults with additional safety, efficacy and

pharmacokinetic data in pediatric patients 12 to 17 years of age [see *Dosage and Administration (3.1)*, *Adverse Reactions (7.1)*, *Clinical Pharmacology (12.3)*, and *Clinical Studies (14.1, 14.2, 14.3, and 14.4)*].

The adverse reaction profile in patients 12 to 17 years of age was similar to adults.

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 in pediatric patients less than 12 years of age based on AUC). 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. The relevance of heart valve thickening in this study to pediatric patients less than 12 years of age is unknown. These findings are not relevant for patients 12 years of age and older. 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.

9.4 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)*].

9.5 Hepatic Impairment

No dosage adjustment for DEXILANT is necessary for patients with mild hepatic impairment (Child-Pugh Class A).

In a study of adult patients with moderate hepatic impairment (Child-Pugh Class B)

who received a single dose of 60 mg DEXILANT, there was a significant increase in systemic exposure of dexlansoprazole compared to healthy subjects with normal hepatic function [see Clinical Pharmacology (12.3)]. Therefore, for patients with moderate hepatic impairment (Child-Pugh Class B), dosage reduction is recommended for the treatment of erosive reflux oesophagitis [see Dosage and Administration (3.2)].

No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C); the use of DEXILANT is not recommended for these patients [see Dosage and Administration (3.2)].

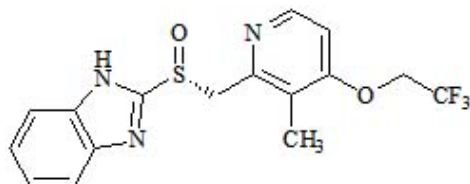
10 OVERDOSAGE

There have been no reports of significant overdose with 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.

11 DESCRIPTION

The active ingredient in DEXILANT (dexlansoprazole modified -release capsules, a proton pump inhibitor, is (+)-2-[(R)-{[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl} sulfinyl]-1H-benzimidazole, a compound that inhibits gastric acid secretion. Dexlansoprazole is the R-enantiomer of lansoprazole (a racemic mixture of the R- and S-enantiomers). Its empirical formula is: 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 modified -release formulation in capsules. The capsules contain dexlansoprazole in a mixture of two types of enteric-coated granules with different pH-dependent dissolution profiles [see Clinical Pharmacology (12.3)].

DEXILANT modified-release capsules are available in two dosage strengths: 30 and 60 mg, per capsule. Each capsule contains enteric-coated granules consisting of dexlansoprazole (active ingredient) and the following inactive ingredients: sucrose, sugar spheres (sucrose, corn starch), talc, methacrylic acid-methyl methacrylate

copolymer (1:2), magnesium carbonate, methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30 per cent (methacrylic acid units, ethyl acrylate units, sodium dodecylsulfate, polysorbate 80), low-substituted hydroxypropyl cellulose, hypromellose, titanium dioxide (E171), methacrylic acid-methyl methacrylate copolymer (1:1), triethyl citrate, macrogol 8000, polysorbate 80, hydroxypropyl cellulose and Silica colloidal anhydrous. The capsule shell is made of hypromellose, carrageenan (E407) and potassium chloride, water, purified. Based on the capsule shell color, blue contains Indigotine (E132); gray contains Iron oxide black (E172); and both contain titanium dioxide (E171). Printing ink: Iron oxide red (E172), iron oxide yellow (E172), indigotine (E132), carnauba wax, shellac, glycerol mono-oleate.

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 (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 5.

Table 5. 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 (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 30 and 60 mg DEXILANT. 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 (6.9)*].

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, 60 or 90 mg 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)*].

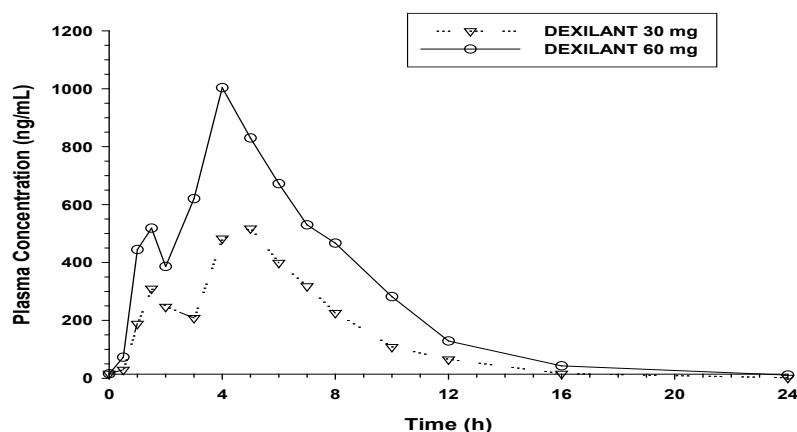
Cardiac Electrophysiology

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 modified-release formulation of DEXILANT 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 GORD. No accumulation of dexlansoprazole occurs after multiple, once daily doses of DEXILANT 30 or 60 mg, 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 Once Daily for 5 Days in Healthy Adult Subjects



The pharmacokinetics of dexlansoprazole are highly variable, with percent coefficient of variation (%CV) values for C_{max} , AUC, and CL/F of greater than 30% (see *Table 6*).

Table 6. Mean (%CV) Pharmacokinetic Parameters for Adult Subjects on Day 5 After Administration of DEXILANT			
Dose (mg)	C_{max} (ng/mL)	AUC₂₄ (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 or 60 mg to healthy subjects and symptomatic GORD patients, mean C_{max} and AUC values of dexlansoprazole increased approximately dose proportionally (*see Figure 1*).

When granules of DEXILANT 60 mg 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 (3.3)*].

Effect on Food

In food-effect studies in healthy subjects receiving DEXILANT 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 (3.3)*].

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 GORD 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, no unchanged dexlansoprazole is excreted in urine. Following the administration of [14C] 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: Pediatric Population

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

Patients 12 to 17 Years of Age

The pharmacokinetics of dexlansoprazole were studied in 36 patients 12 to 17 years of age with symptomatic GORD in a multi-center trial. Patients were randomized to receive DEXILANT 30 or 60 mg once daily for seven days. The dexlansoprazole mean C_{max} and AUC in patients 12 to 17 years of age were 105 and 88%, respectively, compared to those observed in adults at the 30 mg dose, and were 81 and 78%, respectively, at the 60 mg dose (see Tables 6 and 7).

Table 7. Mean (%CV) Pharmacokinetic Parameters in Patients 12 to 17 Years of Age with Symptomatic GORD on Day 7 After Administration of DEXILANT Once Daily for 7 Days			
Dose	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	CL/F (L/h)
30 mg (N=17)	691 (53)	2886 (47)	12.8 (48)
60 mg (N=18)	1136 (51)	5120 (58)	15.3 (49)

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 (9.4)*].

Sex

In a study of 12 male and 12 female healthy subjects who received a single dose of DEXILANT 60 mg, 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 dose of 60 mg DEXILANT 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 (3.2), Use in Specific Populations (9.5)*].

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 co-administered 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 (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 co-administered 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.

12.4 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 or 60 mg (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 one 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 (four 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, two 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 Treatment of erosive reflux oesophagitis in Adults

Two multi-center, double-blind, active-controlled, randomized, eight week studies were conducted in patients with endoscopically confirmed erosive reflux oesophagitis. 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 once daily, DEXILANT 90 mg once daily or lansoprazole 30 mg once 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 erosive reflux oesophagitis (Grades A and B) and 29% of patients had moderate to severe erosive reflux oesophagitis (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 erosive reflux oesophagitis at Week 4 or 8 is presented below in Table 8.

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	70	87	(-1.5, 6.1) [§]

	648	Lansoprazole 30 mg	65	85	
2	639	DEXILANT 60 mg	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 erosive reflux oesophagitis 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 once daily was studied and did not provide additional clinical benefit over DEXILANT 60 mg once daily.

14.2 Maintenance of healed erosive reflux oesophagitis and maintenance of relief of heartburn in Adults

A multi-center, double-blind, placebo-controlled, randomized study was conducted in patients who successfully completed an erosive reflux oesophagitis study and showed endoscopically confirmed healed erosive reflux oesophagitis. Maintenance of healing and symptom resolution over a six month period was evaluated with DEXILANT 30 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.

Sixty-six percent of patients treated with 30 mg of DEXILANT remained healed over the six-month time period as confirmed by endoscopy (*see Table 9*).

Number of Patients (N)[†]	Treatment Group (daily)	Maintenance Rate (%)
125	DEXILANT 30 mg	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 once daily was studied and did not provide additional clinical benefit over DEXILANT 30 mg once daily.

The effect of DEXILANT 30 mg 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 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 erosive reflux oesophagitis between Month 2 and Month 6.

Table 10. Median Percentage of 24 Hour Heartburn-Free Periods of the Maintenance of healed erosive reflux oesophagitis Study in Adults						
	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	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 Treatment of Symptomatic non-erosive GORD in Adults

A multi-center, double-blind, placebo-controlled, randomized, four week study was conducted in patients with a diagnosis of symptomatic non-erosive GORD 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 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 once daily was studied and provided no additional clinical benefit over DEXILANT 30 mg once daily.

Table 11. Median Percentages of 24 Hour Heartburn-Free Periods During the 4 Week Treatment Period of the symptomatic non-erosive GORD Study in Adults		
N	Treatment	Heartburn-Free

	Group (daily)	24 hour Periods (%)
312	DEXILANT 30 mg	54.9*
310	Placebo	18.5

*Statistically significant vs placebo

A higher percentage of patients on DEXILANT 30 mg 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% vs placebo 15%; on Day 28: DEXILANT 63% vs placebo 40%).

14.4 Pediatric GORD

Use of DEXILANT in patients 12 to 17 years of age is supported by evidence from adequate and well-controlled studies of DEXILANT capsules in adults, with additional safety, efficacy, and pharmacokinetic data from studies performed in pediatric patients.

Treatment of erosive reflux oesophagitis, Maintenance of healed erosive reflux oesophagitis and maintenance of relief of Heartburn

In a multi-center, 36 week trial, 62 patients 12 to 17 years of age with a documented history of GORD for at least three months and endoscopically-proven erosive esophagitis (EE) were enrolled to evaluate the healing of erosive reflux esophagitis, maintenance of healed erosive reflux esophagitis and maintenance of relief of heartburn, followed by an additional 12 weeks without treatment. The median age was 15 years, with males accounting for 61% of the patients. Based on the Los Angeles Classification Grading Scale, 97% of patients had mild erosive reflux esophagitis (Grades A and B), and 3% of patients had moderate to severe erosive reflux esophagitis (Grades C and D) before treatment.

In the first eight weeks, 62 patients were treated with DEXILANT 60 mg once daily to evaluate the healing of erosive reflux esophagitis. Of the 62 patients, 58 patients completed the eight week trial, and 51 (88%) patients achieved healing of erosive reflux esophagitis, as confirmed by endoscopy, over eight weeks of treatment (*see Table 12*).

Table 12. Treatment of erosive reflux esophagitis at Week 8 in Pediatric Patients 12 to 17 Years of Age	
	DEXILANT 60 mg
Proportion of randomized patients healed n (%) 95% CI	51/62 (82%) (70, 91) [†]
Proportion of evaluable patients healed* n (%)	51/58 (88%) (77, 95) [†]

95% CI	
--------	--

† Includes only patients who underwent post-baseline endoscopy.

* Reported are the exact confidence limits.

After the initial eight weeks of treatment, all 51 patients with healed erosive reflux esophagitis were randomized to receive treatment with DEXILANT 30 mg or placebo, once daily for an additional 16 weeks to evaluate maintenance of healing and symptom resolution. Maintenance of healing was assessed by endoscopy at Week 24. Of the 51 patients randomized, 13 patients discontinued early. Of these, five patients did not undergo post-baseline endoscopy. Eighteen of 22 (82%) evaluable patients treated with DEXILANT 30 mg remained healed over the 16 week treatment period as confirmed by endoscopy, compared with 14 of 24 (58%) in placebo (*see Table 13*).

Table 13. Maintenance of Healed erosive reflux esophagitis at Week 24* in Pediatric Patients 12 to 17 Years of Age		
	DEXILANT 30 mg	Placebo
Proportion of randomized patients who maintained healing of erosive reflux esophagitis n (%) 95% CI	18/25 (72%) (51, 88) [‡]	14/26 (54%) (33, 73) [‡]
Proportion of evaluable patients who maintained healing of erosive reflux esophagitis [†] n (%) 95% CI	18/22 (82%) (60, 95) [‡]	14/24 (58%) (37, 78) [‡]

* Following eight weeks of initial therapy and 16 weeks of maintenance therapy.

† Includes patients with at least one post-baseline endoscopy.

‡ Reported are the exact confidence limits.

Relief of heartburn was assessed in randomized patients during the 16 week maintenance period. The median percentage of 24-hour heartburn-free periods was 87% for those receiving DEXILANT 30 mg compared to 68% for those receiving placebo.

Out of the 32 patients who maintained healing of erosive reflux esophagitis at the end of the 16 week maintenance period, 27 patients (16 treated with DEXILANT and 11 treated with placebo during the double-blind phase) were followed for an additional 12 weeks without therapy. Twenty four of the 27 patients completed the 12-week follow-up period. One patient required treatment with acid suppression therapy.

Treatment of Symptomatic Non-Erosive GORD

In a single-arm, open-label, multi-center trial, 104 pediatric patients 12 to 17 years of age with symptomatic non-erosive GORD were treated with DEXILANT 30 mg once daily, for four weeks to evaluate safety and effectiveness. Patients had a documented history of GORD symptoms for at least three months prior to screening, reported heartburn on at least three out of seven days during screening, and had no esophageal erosions as confirmed by endoscopy. The median age was 15 years, with females accounting for 70% of the patients. During the four week treatment period, the median percentage of 24-hour heartburn free periods was 47%.

15 HOW SUPPLIED/STORAGE AND HANDLING

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

PVC/PE/polychlorotrifluoroethylene (PCTFE) - aluminium blister packs containing 14 or 28 capsules.

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

PVC/PE/polychlorotrifluoroethylene (PCTFE) - aluminium blister packs containing 14 or 28 capsules.

Not all pack sizes may be marketed.

Do not store above 25°C.

The expiry date of the product is indicated on the packaging materials.

16 MANUFACTURER

Takeda GmbH,
Byk-Gulden-Straße 2,
78467 Konstanz,
Germany

17 REGISTRATION HOLDER

Takeda Israel Ltd.
Efal 25,
P.O.B 4140,
Petach Tikva 4951125

18 REGISTRATION NUMBER(S)

Dexilant 30 mg - 155-45-34383
Dexilant 60 mg - 155-46-34387

Revised in April 2022 according to MOHs guidelines

Based on US PI update from March 2022

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