(เอกสารกำกับยาภาษาอังกฤษฉบับใหม่)

DEXILANT®
(Dexlansoprazole) Delayed release capsules

DOSAGE FORM AND STRENGTH

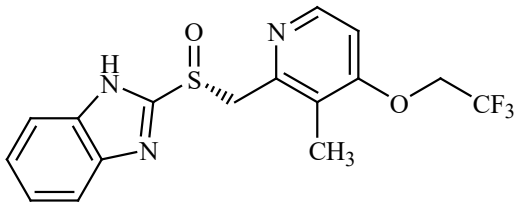
DEXILANT® delayed release capsules, 30 mg, are capsules with blue opaque cap printed with "TAP" logo in dark gray and gray opaque body printed with "30" in dark gray containing white to nearly white granules. Each capsule contains dexlansoprazole 30 mg.

DEXILANT® delayed release capsules, 60 mg, are capsules with blue opaque cap printed with "TAP" logo in dark gray and blue opaque body printed with "60" in dark gray containing white to nearly white granules. Each capsule contains dexlansoprazole 60 mg.

PRODUCT DESCRIPTION

The active ingredient in DEXILANT® (dexlansoprazole) delayed release capsules, a proton pump inhibitor, is (+)-2-[(*R*)-{[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl] methyl} sulfinyl]-*1H*-benzimidazole, a compound that inhibits gastric acid secretion. Dexlansoprazole is the *R*-enantiomer of lansoprazole (a racemic mixture of the *R*- and *S*-enantiomers).
Its empirical formula is: $C_{16}H_{14}F_3N_3O_2S$, with a molecular weight of 369.36.

Dexlansoprazole has the following chemical structure:



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

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

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

DEXILANT® is available in two dosage strengths: 30 mg and 60 mg, per capsule. Each capsule contains enteric-coated granules consisting of dexlansoprazole (active ingredient).

INDICATIONS

1. Healing of Erosive Esophagitis

DEXILANT® is indicated in patients 12 years of age and older for healing of all grades of erosive esophagitis (EE) for up to eight weeks.

2. Maintenance of Healed Erosive Esophagitis and Relief of Heartburn
DEXILANT® is indicated in patients 12 years of age and older to maintain healing of EE and relief of heartburn for up to six months in adults and 16 weeks in patients 12 to 17 years of age.

3. Treatment of Symptomatic Non-Erosive Gastroesophageal Reflux Disease
DEXILANT® is indicated in patients 12 years of age and older for the treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for four weeks.

DOSAGE AND ADMINISTRATION

1. Recommended Dosage in Patients 12 Years of Age and Older

Table 1: Recommended DEXILANT® Dosage Regimen by Indication in Patients 12 Years of Age and Older

Indication	Dosage of DEXILANT® Capsules	Duration
Healing of EE	One 60 mg capsule once daily	Up to 8 weeks
Maintenance of Healed EE and relief of heartburn	One 30 mg capsule once daily	Controlled studies did not extend beyond 6 months in adults and 16 weeks in patients 12 to 17 years of age.
Symptomatic Non-Erosive GERD	One 30 mg capsule once daily	4 weeks

2. Dosage Adjustment in Patients with Hepatic Impairment for the Healing of EE

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

3. Important Administration Information
Missed doses: If a dose is missed, administer as soon as possible. However, if the next scheduled dose is due, do not take the missed dose, and take the next dose on time. Do not take two doses at one time to make up for a missed dose.

DEXILANT® Delayed Release Capsules

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

CONTRAINDICATIONS

DEXILANT® is contraindicated in patients with known hypersensitivity to any component of the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute tubulointerstitial nephritis and urticaria *[see Warnings and Precautions (2), Adverse Drug Reactions]*.

PPIs, including DEXILANT®, are contraindicated with rilpivirine-containing products *[see Drug Interactions].*

WARNINGS AND PRECAUTIONS

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.

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]*.

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 Drug Reactions].*

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

4. Bone Fracture

Several published observational studies suggest that proton pump inhibitor (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 Dosage and Administration and Adverse Drug Reactions].*

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 Drug Reactions]. Discontinue DEXILANT at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

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 4 to 12 weeks.

Serological testing (e.g., ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

7. Cyanocobalamin (Vitamin B-12) Deficiency

Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed in patients treated with DEXILANT®.

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 Drug Reactions*].

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.

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, Clinical Pharmacology].*

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].*

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.

12 Risk of Heart Valve Thickening in Pediatric Patients Less Than Two Years of Age

DEXILANT is not recommended in pediatric patients less than two years of age. Nonclinical studies in juvenile rats with lansoprazole have demonstrated an adverse effect of heart valve thickening. Dexlansoprazole is the R-enantiomer of lansoprazole *[see Use in Specific Populations]*

DRUG INTERACTIONS

Tables 2 and 3 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 2: Clinically Relevant Interactions Affecting Drugs Co-Administered with DEXILANT® and Interactions with Diagnostics

Antiretrovirals	
Clinical Impact:	The effect of PPIs on antiretroviral drugs is variable. The clinical importance and the mechanisms behind these interactions are not always known. • Decreased exposure of some antiretroviral drugs (e.g., rilpivirine, atazanavir, and nelfinavir) when used concomitantly with dexlansoprazole may reduce antiviral effect and promote the development of drug resistance. • Increased exposure of other antiretroviral drugs (e.g., saquinavir) when used concomitantly with dexlansoprazole may increase toxicity of the antiretroviral drugs. • There are other antiretroviral drugs which do not result in clinically relevant interactions with dexlansoprazole.
Intervention:	Rilpivirine-containing products: Concomitant use with DEXILANT® is contraindicated *[see Contraindications]*. See prescribing information. Atazanavir: See prescribing information for atazanavir for dosing information. Nelfinavir: Avoid concomitant use with DEXILANT®. See prescribing information for nelfinavir. Saquinavir: See the prescribing information for saquinavir and monitor for potential saquinavir toxicities. Other antiretrovirals: See prescribing information.
Warfarin	
Clinical Impact:	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.
Intervention:	Monitor INR and prothrombin time. Dose adjustment of warfarin may be needed to maintain target INR range. See prescribing information for warfarin.
Methotrexate	
Clinical Impact:	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 Warnings and Precautions(10)].*
Intervention:	A temporary withdrawal of DEXILANT® may be considered in some patients receiving high-dose methotrexate.
Digoxin	
Clinical Impact:	Potential for increased exposure of digoxin.

Intervention:	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, mycophenoloate mofetil, ketoconazole/itraconazole)	
Clinical Impact:	Dexlansoprazole can reduce the absorption of other drugs due to its effect on reducing intragastric acidity.
Intervention:	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	
Clinical Impact:	Potentially increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.
Intervention:	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	
Clinical Impact:	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 Warnings and Precautions (9), Clinical Pharmacology].*
Intervention:	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	
Clinical Impact:	Hyper-response in gastrin secretion in response to secretin stimulation test, falsely suggesting gastrinoma.
Intervention:	Temporarily stop DEXILANT® treatment at least 30 days before assessing to allow gastrin levels to return to baseline *[see Clinical Pharmacology].*
False Positive Urine Tests for THC	
Clinical Impact:	There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs.
Intervention:	An alternative confirmatory method should be considered to verify positive results.

Table 3: Clinically Relevant Interactions Affecting DEXILANT® When Co-Administered with Other Drugs

CYP2C19 or CYP3A4 Inducers	
Clinical Impact:	Decreased exposure of dexlansoprazole when used concomitantly with strong inducers *[see Clinical Pharmacology].*
Intervention:	St. John's Wort, rifampin: Avoid concomitant use with DEXILANT®. Ritonavir-containing products: See prescribing information.
CYP2C19 or CYP3A4 Inhibitors	
Clinical Impact:	Increased exposure of dexlansoprazole is expected when used concomitantly with strong inhibitors *[see Clinical Pharmacology].*
Intervention:	Voriconazole: See prescribing information.

USE IN SPECIFIC POPULATIONS

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 a 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 2-4% and 15-20%, 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 9 times the maximum recommended human dexlansoprazole dose (60 mg per 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.

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.

3. Pediatric Use

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

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. The adverse reaction profile in patients 12 to 17 years of age was similar to adults *[see Dosage and Administration, Adverse Drug Reactions, Clinical Pharmacology, Clinical Studies].*

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 two years of age *[see Warnings and Precautions]*. Nonclinical studies in juvenile rats treated with lansoprazole (the racemic mixture) have demonstrated adverse effects of heart valve thickening and bone changes at dexlansoprazole exposures which are expected to be similar to or higher than the dexlansoprazole exposure in pediatric patients one year to two years of age, as described below in *Juvenile Animal Toxicity Data*.
The use of DEXILANT is not recommended for the treatment of symptomatic GERD in pediatric patients one month to less than one year of age because lansoprazole was not shown to be effective in a multicenter, double-blind controlled trial.

Juvenile Animal Toxicity Data

Heart Valve Thickening
In
two oral toxicity studies, thickening of the mitral heart valve occurred in juvenile rats treated with lansoprazole. Heart valve thickening was observed primarily with oral dosing initiated on postnatal Day 7 (age equivalent to neonatal humans) and postnatal Day 14 (human age equivalent of approximately one year) at doses of 250 mg/kg/day and higher (at postnatal Day 7 and postnatal Day 14 respectively, 2.5 and 1.8 times the expected dexlansoprazole exposure based on AUC in pediatric patients one year to two years of age). The treatment durations associated with heart valve thickening ranged from 5 days to 8 weeks. The findings reversed or trended towards reversibility after a 4-week drug-free recovery period. The incidence of heart valve thickening after initiation of dosing on postalnatal Day 21 (human age equivalent of approximately two years) was limited to a single rat (1/24) in groups given 500 mg/kg/day for 4 or 8 weeks (2.1 times the expected dexlansoprazole exposure based on AUC in pediatric pateints one year to two years of age). Based on the low incidence of heart valve thickening in 21-day old rats and the equivalent human age, the risk of heart valve injury dose not appear to be relevant to patients two years of age and older.

Bone Changes

In an eight-week oral toxicity study of lansoprazole in juvenile rats
with dosing initiated on postnatal Day 7, doses equal to or greater than 100 mg/kg/day (dexlansoprazole exposure based on AUC approximately equal to that in pediatric patients one year to two years of age) 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 four-week recovery period. Longer term data were not collected.

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]*.

5. Hepatic Impairment

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

In a study of patients with moderate hepatic impairment (Child-Pugh Class B) who received a single 60 mg DEXILANT®, there was a significant increase in systemic exposure of dexlansoprazole compared to healthy subjects with normal hepatic function *[see Clinical Pharmacology].* Therefore, for adult patients with moderate hepatic impairment (Child-Pugh Class B), the recommended dosage of DEXILANT® for the healing of EE is 30 mg once daily for up to 8 weeks *[see Dosage and Administration].*

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].*

ADVERSE DRUG REACTIONS

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

- Acute Tubulointerstitial Nephritis [see Warnings and Precautions (2)]
- *Clostridium difficile*-Associated Diarrhea [see Warnings and Precautions (3)]
- Bone Fracture [see Warnings and Precautions (4)]
- Severe Cutaneous Adverse Reactions [see Warnings and Precautions (5)]
- Cutaneous and Systemic Lupus Erythematosus [see Warnings and Precautions (6)]
- Cyanocobalamin (Vitamin B-12) Deficiency [see Warnings and Precautions (7)]
- Hypomagnesemia and Mineral Metabolism [see Warnings and Precautions (8)]
- Fundic Gland Polyps [see Warnings and Precautions (11)]
- Risk of Heart Valve Thickening in Pediatric Patients Less than Two Years of Age [see Warnings and Precautions (12)]

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 patients in controlled and uncontrolled clinical

studies, including 863 patients treated for at least 6 months and 203 patients treated for one year. Patients ranged in age from 18 to 90 years (median age 48 years), with 54% female, 85% Caucasian, 8% Black, 4% Asian, and 3% other races. Six randomized controlled clinical trials were conducted for the treatment of EE, maintenance of healed EE, and symptomatic GERD, which included 896 patients on placebo, 455 patients on DEXILANT® 30 mg, 2218 patients on DEXILANT® 60 mg, and 1363 patients on lansoprazole 30 mg once daily.

Common Adverse Reactions

The most common adverse reactions (≥2%) that occurred at a higher incidence for DEXILANT® than placebo in the controlled studies are presented in Table 4.

Table 4: Common Adverse Reactions in Controlled Studies

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® therapy was diarrhea (0.7%).

Less common Adverse Reactions

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

Blood and Lymphatic System Disorders: anemia, lymphadenopathy

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

Ear and Labyrinth Disorders: ear pain, tinnitus, vertigo

Endocrine Disorders: goiter

Eye Disorders: eye irritation, eye swelling

Gastrointestinal Disorders: abdominal discomfort, abdominal tenderness, abnormal feces, anal discomfort, Barrett's esophagus, bezoar, bowel sounds abnormal, breath odor, colitis microscopic, colonic polyp, constipation, dry mouth, duodenitis, dyspepsia, dysphagia, enteritis, eructation,

esophagitis, gastric polyp, gastritis, gastroenteritis, gastrointestinal disorders, gastrointestinal hypermotility disorders, GERD, GI ulcers and perforation, hematemesis, hematochezia, hemorrhoids, impaired gastric emptying, irritable bowel syndrome, mucus stools, oral mucosal blistering, painful defecation, proctitis, paresthesia oral, rectal hemorrhage, retching

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

Hepatobiliary Disorders: biliary colic, cholelithiasis, hepatomegaly

Immune System Disorders: hypersensitivity

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

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

Laboratory Investigations: ALP increased, ALT increased, AST increased, bilirubin decreased/increased, blood creatinine increased, blood gastrin increased, blood glucose increased, blood potassium increased, liver function test abnormal, platelet count decreased, total protein increased, weight increase

Metabolism and Nutrition Disorders: appetite changes, hypercalcemia, hypokalemia

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

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

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

Renal and Urinary Disorders: dysuria, micturition urgency

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

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

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

Vascular Disorders: deep vein thrombosis, hot flush, hypertension

Additional adverse reactions that were reported in a long-term uncontrolled study[1)] 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 GERD, healing of EE, maintenance of healed EE and relief of heartburn *[see Clinical Studies].*

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.

Other adverse reactions

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

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

General Disorders and Administration Site Conditions: facial edema

Hepatobiliary Disorders: drug-induced hepatitis

Immune System Disorders: anaphylactic shock (requiring emergency intervention), exfoliative dermatitis, SJS/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

OVERDOSAGE

There have been no reports of significant overdose of DEXILANT®. Multiple doses of DEXILANT® 120 mg and a single dose of DEXILANT® 300 mg did not result in death or other severe adverse events. However, serious adverse events of hypertension have been reported in association with twice daily doses of DEXILANT® 60 mg. Non-serious adverse reactions observed with twice daily doses of DEXILANT® 60 mg include hot flashes, contusion, oropharyngeal pain, and weight loss. Dexlansoprazole is not expected to be removed from the circulation by hemodialysis. In the event of over-exposure, treatment should be symptomatic and supportive.

CLINICAL PHARMACOLOGY

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.

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 DEXILANT® on serum gastrin concentrations was evaluated in approximately 3460 patients in clinical trials up to 8 weeks and in 1023 patients for up to 6 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 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.

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 (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 per kg per day of lansoprazole,

marked hypergastrinemia was observed followed by ECL cell proliferation and formation of carcinoid tumors, especially in female rats *[see Nonclinical Toxicology]*.

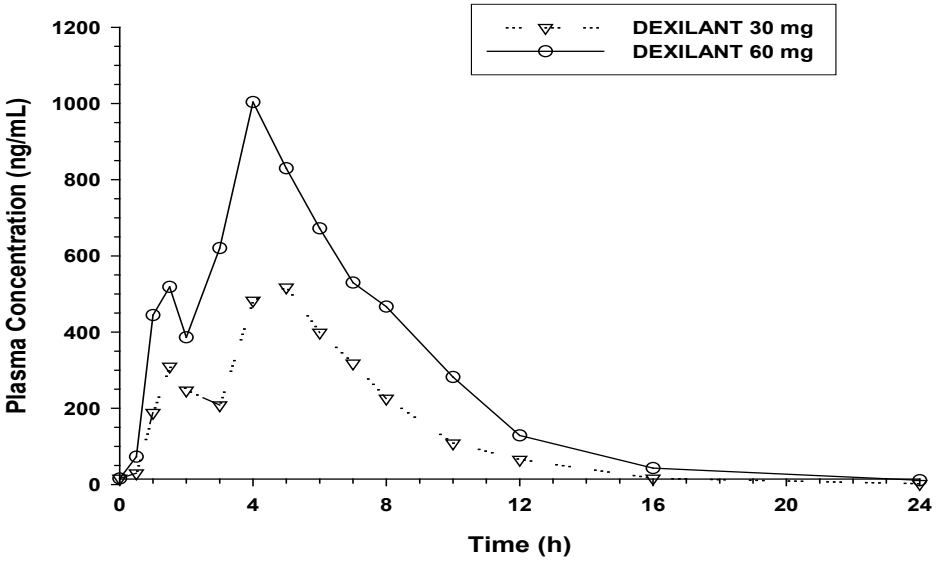
Cardiac Electrophysiology

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

3. Pharmacokinetics

The dual delayed release formulation of DEXILANT® 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). Dexlansoprazole is eliminated with a half-life of approximately 1 to 2 hours in healthy subjects and in patients with symptomatic GERD. 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 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 Subjects on Day 5 After Administration of DEXILANT®

Dose (mg)	C_{max} (ng/mL)	AUC_{24} (ng·h/mL)	CL/F (L/h)
30	658 (40%)	3275 (47%)	11.4 (48%)

	(N=44)	(N=43)	(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 GERD 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]*

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].*

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 per mL. The apparent volume of distribution (Vz/F) after multiple doses in symptomatic GERD patients was 40 L.

Elimination

Metabolism

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

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

Excretion

Following the administration of DEXILANT®, 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/hour, respectively, after 5-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 GERD in a multi-center trial. Patients were randomized to receive DEXILANT® 30 or 60 mg capsules 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 GERD on Day 7 After Administration of DEXILANT Capsules 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].*

Sex

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

Renal Impairment

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

Hepatic Impairment

In a study of 12 patients with moderate hepatic impairment (Child-Pugh Class B) who received a single dose of DEXILANT® 60 mg, the systemic exposure (AUC) of bound and unbound dexlansoprazole 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. No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C) *[see Dosage and Administration, Use in Specific Populations].*

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]*.

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 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 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. No dose adjustment of clopidogrel is necessary when administered with an approved dose of DEXILANT®.

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.

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 2 times higher in intermediate compared to extensive metabolizers; in poor metabolizers, mean C_{max} was up to 4 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.

NONCLINICAL TOXICOLOGY

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 per kg per 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 body surface area (BSA)] given the recommended human dose of lansoprazole 30 mg per day.

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

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 per kg per day (4 to 40 times the recommended human lansoprazole dose based on BSA) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with lansoprazole doses of 15 to 600 mg per kg per day, 2 to 80 times the recommended human lansoprazole dose based on BSA. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg lansoprazole per kg per day (40 to 80 times the recommended human lansoprazole dose based on BSA) and female mice treated with 150 to 600 mg lansoprazole per kg per 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 per kg per 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 per kg per 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.

CLINICAL STUDIES

1. Healing of Erosive Esophagitis in Adults

Two multi-center, double-blind, active-controlled, randomized, 8-week studies were conducted in patients with endoscopically confirmed EE [2)-3)]. 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 EE (Grades A and B) and 29% of patients had moderate to severe EE (Grades C and D) before treatment.

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

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

Table 8: EE Healing Rates[a]: All Grades

Study	Number of Patients (N)[b]	Treatment Group (daily)	Week 4 % Healed	Week 8[c] % Healed	(95% CI) for the Treatment Difference (DEXILANT®– Lansoprazole) by Week 8
1[2)]	657	DEXILANT® 60 mg	70	87	(-1.5, 6.1)[d]
	648	Lansoprazole 30 mg	65	85	
2[3)]	639	DEXILANT® 60 mg	66	85	(2.2, 10.5)[d]
	656	Lansoprazole 30 mg	65	79	

CI = Confidence interval
[a] Based on crude rate estimates, patients who did not have endoscopically documented healed EE and prematurely discontinued were considered not healed.
[b] Patients with at least one post baseline endoscopy
[c] Primary efficacy endpoint
[d] 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.

2. Maintenance of Healed Erosive Esophagitis and Relief of Heartburn in Adults

A multi-center, double-blind, placebo-controlled, randomized study was conducted in patients who successfully completed an EE study and showed endoscopically confirmed healed EE[4)]. 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).

Table 9: Maintenance Rates[a] of Healed EE at Month 6 in Adults

Number of Patients (N)[b]	Treatment Group (daily)	Maintenance Rate (%)
125	DEXILANT® 30 mg	66.4[c]
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
[c] 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 6-month treatment period. (see Table 10). The majority of patients treated with placebo discontinued due to relapse of EE between Month 2 and Month 6.

Table 10: Median Percentage of 24-Hour Heartburn-Free Periods of the Maintenance of Healed EE Study in Adults

	Overall Treatment[a]		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[b]	126	96.7	80	98.3
Placebo	141	28.6	117	28.6	23	73.3

[a] Secondary efficacy endpoint
[b] Statistically significant vs placebo

3. Treatment of Symptomatic Non-Erosive GERD in Adults

A multi-center, double-blind, placebo-controlled, randomized, 4-week study was conducted in patients with a diagnosis of symptomatic non-erosive GERD made primarily by presentation of symptoms[5)]. 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.

DEXILANT® 30 mg provided statistically significantly greater percent of days with heartburn-free 24-hour periods over placebo as assessed by daily diary over 4 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 GERD Study in Adults

N	Treatment Group (daily)	Heartburn-Free 24-hour Periods (%)
312	DEXILANT® 30 mg	54.9[a]
310	Placebo	18.5

[a] 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%).

4. Pediatric GERD

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

Healing of EE, Maintenance of Healed EE and Relief of Heartburn

In a multi-center, 36-week trial, 62 patients 12 to 17 years of age with a documented history of GERD for at least three months and endoscopically-proven erosive esophagitis (EE) were enrolled to evaluate the healing of EE, maintenance of healed EE and 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 EE (Grades A and B), and 3% of patients had moderate to severe EE (Grades C and D) before treatment.

In the first 8 weeks, 62 patients were treated with DEXILANT® 60 mg capsules once daily to evaluate the healing of EE. Of the 62 patients, 58 patients completed the 8 week trial, and 51 (88%) patients achieved healing of EE, as confirmed by endoscopy, over 8 weeks of treatment (*see Table 12*).

Table 12. Healing of EE 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 (%) 95% CI	51/58 (88%) (77, 95)*

† 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 EE 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, 5 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 EE at Week 24* in Pediatric Patients 12 to 17 Years of Age

	DEXILANT® 30 mg capsules	Placebo
Proportion of randomized patients who maintained healing of EE n (%) 95% CI	18/25 (72%) (51, 88)†	14/26 (54%) (33, 73)†
Proportion of evaluable patients who maintained healing of EE** n (%) 95% CI	18/22 (82%) (60, 95)†	14/24 (58%) (37, 78)†

*Following 8 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 EE 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 GERD

In a single-arm, open-label, multi-center trial, 104 pediatric patients 12 to 17 years of age with symptomatic non-erosive GERD were treated with DEXILANT® 30 mg once daily, for 4 weeks to evaluate safety and effectiveness. Patients had a documented history of GERD symptoms for at least three months prior to screening, reported heartburn on at least 3 out of 7 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 4 week treatment period, the median percentage of 24 hour heartburn free periods was 47%.

STORAGE

Store below 30°C

PACKAGING

Aluminium blister, one blister contains 7 capsules.

References:
1). Study No. T-GI04-88
2). Study No. T-EE04-085
3). Study No. T-EE04-084
4). Study No. T-EE05-135
5). Study No. T-GD05-137

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