PRODUCT MONOGRAPH

^{Pr}DEXILANT®

Dexlansoprazole

delayed release capsules 30 mg and 60 mg

H^+, K^+ - ATPase Inhibitor

Takeda Canada Inc.
Oakville, Ontario, L6M 4X8

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Dexlansoprazole delayed release capsules, 30 mg and 60 mg

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Delayed Release Capsule 30 mg, 60 mg	None *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section*.

INDICATIONS AND CLINICAL USE

DEXILANT® is indicated for the following in adults 18 years of age and older:

Healing of Erosive Esophagitis
DEXILANT® is indicated for healing of all grades of erosive esophagitis for up to 8 weeks.

Maintenance of Healed Erosive Esophagitis
DEXILANT® is indicated for maintaining healing of erosive esophagitis for up to 6 months.

Symptomatic Non-Erosive Gastroesophageal Reflux Disease
DEXILANT® is indicated for the treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for 4 weeks.

Geriatrics (> 65 years of age):
No dosage adjustment is necessary for elderly patients.

Pediatrics (< 18 years of age):
Safety and effectiveness of DEXILANT® in pediatric patients have not been established.

CONTRAINDICATIONS
Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

DEXILANT® should not be concomitantly administered with atazanavir (see DRUG INTERACTIONS, Drugs with pH-Dependent Absorption Pharmacokinetics).

WARNINGS AND PRECAUTIONS

General

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

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

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

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

Decreased gastric acidity due to any means, including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors (PPIs) may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly *Clostridium difficile*.

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. A temporary withdrawal of the PPI may be considered in some patients receiving treatments with high dose methotrexate.

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 REACTIONS**).

Carcinogenesis and Mutagenesis

Dexlansoprazole was positive in the Ames test for mutagenicity in bacteria. In an *in vitro* chromosome aberration test using Chinese hamster lung cells, dexlansoprazole was considered positive based on equivocal data in which the percentage of cells with aberrant chromosomes increased slightly but did not reach the preset criteria for a positive response. Dexlansoprazole was negative in the *in vivo* mouse micronucleus test.

Lansoprazole is a racemic mixture of R- and S-enantiomers. Following administration of lansoprazole in humans and animals, the major component circulating in plasma is dexlansoprazole, the R-enantiomer of lansoprazole. Therefore, the carcinogenic potential of dexlansoprazole was assessed using existing lansoprazole studies (see **TOXICOLOGY**). Lansoprazole treatment for 2-years was associated with hyperplasia and neoplasms (carcinoids) of enterochromaffin-like cells (ECL cells) in the stomach of conventional rats and mice. These proliferations are related to prolonged hypergastrinemia secondary to gastric acid suppression. Benign tumors of the testis (interstitial cell adenomas in rats and rete testis adenomas in mice) were secondary to an inhibitory effect on testosterone synthesis at high doses in these species. Hepatocellular adenomas and carcinomas were increased in the livers of mice related to induction of CYP enzymes leading to increased liver weights.

Endocrine and 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. 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**).

The chronic use of PPIs may lead to hypomagnesaemia. Moreover, hypokalemia and hypocalcemia have been reported in the literature as accompanying electrolyte disorders.

Cyanocobalamin (Vitamin B12) Deficiency

The prolonged use of proton pump inhibitors may impair the absorption of protein-bound Vitamin B12 and may contribute to the development of cyanocobalamin (Vitamin B12) deficiency.

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

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

Special Populations

Pregnant Women:
There are no adequate or well-controlled studies in pregnant women with DEXILANT®. Exposure in clinical trials was very limited. DEXILANT® should not be administered to pregnant women unless the expected benefits outweigh the potential risks. See **TOXICOLOGY, *Reproduction and Teratology*.**

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

Pediatrics (< 18 years of age):
Safety and effectiveness of DEXILANT® in pediatric patients have not been established.

Geriatrics (> 65 years of age):
In clinical studies of DEXILANT®, 11% of patients were aged 65 years and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. No dosage adjustment is necessary for elderly patients. See **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**.
Benefits of use of PPIs should be weighed against the increased risk of fractures as patients in this category (> 71 years of age) may already be at high risk for osteoporosis-related fractures. If the use of PPIs is required, they should be managed carefully according to established treatment guidelines (see **DOSAGE AND ADMINISTRATION** and **ADVERSE REACTIONS**)

Hepatic Impairment:
No dosage adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). A maximum daily dose of 30 mg should be considered for patients with moderate hepatic impairment (Child-Pugh Class B). No studies have been conducted in patients with severe hepatic impairment. See **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**.

Renal Impairment
No dosage adjustment is necessary for patients with renal impairment. See **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of DEXILANT® was evaluated in 4548 patients in controlled and uncontrolled clinical studies (30 mg, 60 mg, and 90 mg), including 863 patients treated for at least 6 months and 282 patients treated for one year. Patients ranged in age from 18 to 90 years (median age 48 years), with 54% female, 85% Caucasian, 8% Black, 4% Asian and 3% other races. Six randomized controlled clinical trials were conducted for the treatment of erosive esophagitis, maintenance of

healed erosive esophagitis, and symptomatic GERD, which included 896 patients on placebo, 2621 patients on DEXILANT® 30 mg or 60 mg and 1363 patients on lansoprazole 30 mg.

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

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

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

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

Body System Adverse Event	**DEXILANT® 60 mg (N=2621) n (%)**	**Lansoprazole 30 mg (N=1363) n (%)**
Gastrointestinal disorders		
Diarrhea	44 (3.2)	28 (2.1)
Abdominal pain	21 (1.5)	19 (1.4)
Nausea	14 (1.0)	18 (1.3)
Nervous system disorders		
Headache	16 (1.2)	19 (1.4)

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

Less Common Clinical Trial Adverse Drug Reactions (<1%)

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

Blood and Lymphatic System Disorders: anemia, lymphadenopathy

Cardiac Disorders: acute myocardial infarction, angina, arrhythmia, bradycardia, edema, palpitations, tachycardia

Ear and Labyrinth Disorders: ear pain, tinnitus, vertigo

Endocrine Disorders: goiter

Eye Disorders: eye irritation, eye swelling

Gastrointestinal Disorders: abdominal discomfort, abdominal tenderness, abnormal feces, anal discomfort, Barrett's esophagus, bezoar, bowel sounds abnormal, breath odor, colitis microscopic, colonic polyp, dry mouth, duodenitis, dyspepsia, dysphagia, enteritis, eructation, esophagitis, gastric polyp, gastritis, gastroenteritis, gastrointestinal disorders, gastrointestinal hypermotility disorders, GERD, GI ulcers and perforation, hematemesis, hematochezia, hemorrhoids, impaired gastric emptying, irritable bowel syndrome, mucus stools, oral mucosal blistering, painful defecation, paresthesia oral, proctitis, rectal hemorrhage, vomiting

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

Hepatobiliary Disorders: biliary colic, cholelithiasis, hepatomegaly

Immune System Disorders: hypersensitivity

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

Injury, Poisoning and Procedural Complications: overdose, procedural pain, sunburn *Laboratory Investigations*: ALP increased, ALT increased, AST increased, bilirubin decreased/increased, blood creatinine increased, blood gastrin increased, blood glucose increased, blood potassium increased, liver function test abnormal, platelet count decreased, total protein increased, weight increased

Metabolism and Nutrition Disorders: appetite changes, hypercalcemia, hypokalemia

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

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

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

Renal and Urinary Disorders: dysuria, micturition urgency

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

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

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

Vascular Disorders: deep vein thrombosis, hot flush, hypertension

Additional adverse reactions that were reported for DEXILANT® (60 mg or 90 mg) in a long-term uncontrolled study included: anaphylaxis, auditory hallucination, B-cell lymphoma, bursitis, central obesity, cholecystitis acute, decreased hemoglobin, dehydration, diabetes mellitus, dysphonia, epistaxis, folliculitis, gout, herpes zoster, hyperglycemia, hyperlipidemia, hypothyroidism, increased neutrophils, MCHC decreased, neutropenia, oral soft tissue disorder, rectal tenesmus, restless legs syndrome, somnolence, thrombocythemia, tonsillitis.

Post-Market Adverse Drug Reactions

Adverse reactions have been identified during post-marketing surveillance of DEXILANT®. As these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura
Ear and Labyrinth Disorders: deafness
Eye Disorders: blurred vision
Gastrointestinal Disorders: oral edema, pancreatitis
General Disorders and Administration Site Conditions: facial edema
Hepatobiliary Disorders: drug-induced hepatitis
Immune System Disorders: anaphylactic shock (requiring emergency intervention), exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal)
Metabolism and Nutritional Disorders: hypomagnesemia, hyponatremia
Musculoskeletal and Connective Tissue: Osteoporosis and osteoporosis-related fractures
Nervous System Disorders: cerebrovascular accident, transient ischaemic attack
Renal and Urinary Disorders: acute renal failure
Respiratory, Thoracic and Mediastinal Disorders: pharyngeal edema, throat tightness
Skin and Subcutaneous Tissue Disorders: generalized rash, leucocytoclastic vasculitis

Withdrawal of long-term PPI therapy can lead to aggravation of acid related symptoms and may result in rebound acid hypersecretion.

DRUG INTERACTIONS

Drug-Drug Interactions

Drugs with pH-Dependent Absorption Pharmacokinetics
DEXILANT® causes inhibition of gastric acid secretion. DEXILANT® is likely to substantially decrease the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, DEXILANT® should not be co-administered with atazanavir.

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

Cytochrome P 450 Interactions
DEXILANT® is metabolized, in part, by CYP2C19 and CYP3A4 (see **ACTION AND CLINICAL PHARMACOLOGY, Metabolism**).

In vitro studies have shown that dexlansoprazole is not likely to inhibit CYP isoforms 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1 or 3A4. As such, no clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Furthermore, *in vivo* studies showed that DEXILANT® did not have an impact on the pharmacokinetics of, coadministered phenytoin (CYP2C9 substrate) or theophylline (CYP1A2 substrate).[1] 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).

Warfarin
In a study of 20 healthy subjects, co-administration of DEXILANT® 90 mg once daily for 11 days with a single 25 mg oral dose of warfarin on day 6 did not result in any significant differences in the pharmacokinetics of warfarin or INR compared to administration of warfarin with placebo.[1] However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Patients treated with PPIs and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Concomitant Use of Antacids with DEXILANT®
No formal drug-drug interaction studies were conducted with DEXILANT® and antacids. Drug-drug interactions studies were performed with the racemate lansoprazole and antacids. Simultaneous administration of lansoprazole with aluminum and magnesium hydroxide or magaldrate results in lower peak plasma levels, but does not significantly reduce bioavailability. Antacids may be used concomitantly if required. In clinical trials, antacids were administered concomitantly with lansoprazole delayed-release capsules. In a single-dose crossover study when 30 mg of lansoprazole was administered concomitantly with one gram of sucralfate in healthy volunteers, absorption of lansoprazole was delayed and its bioavailability was reduced. The value of lansoprazole AUC was reduced by 17% and that for C_{max} was reduced by 21%. In a similar study when 30 mg of lansoprazole was administered concomitantly with 2 grams of sucralfate, lansoprazole AUC and C_{max} were reduced by 32% and 55%, respectively. When lansoprazole dosing occurred 30 minutes prior to sucralfate administration, C_{max} was reduced by only 28% and there was no statistically significant difference in lansoprazole AUC. Therefore, lansoprazole should be administered at least 30 minutes prior to sucralfate. It would be expected that similar results would be seen with DEXILANT®.

Theophylline
Although a study of the use of concomitant theophylline and dexlansoprazole did not reveal any changes in the pharmacokinetics or pharmacodynamics of theophylline, individual patients should monitor their theophylline level while taking the two drugs concomitantly.

Tacrolimus
Concomitant administration of dexlansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.

Clopidogrel
Concomitant administration of dexlansoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition (see **DETAILED PHARMACOLOGY**). No dose adjustment of clopidogrel is necessary when administered with an approved dose of DEXILANT®.

Methotrexate
Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted.

Drug-Food Interactions
DEXILANT® can be taken without regard to food or timing of food (see **ACTION AND CLINICAL PHARMACOLOGY**).

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Tests
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Indication	Recommended Dose	Frequency
Healing of Erosive Esophagitis	60 mg	Once daily for up to 8 weeks
Maintenance of Healed Erosive Esophagitis	30 mg [a]	Once daily [b]
Symptomatic Non-Erosive Gastroesophageal Reflux Disease (GERD)	30 mg	Once daily for 4 weeks

[a] In patients who had moderate or severe erosive esophagitis, a maintenance dose of 60 mg may be used.
[b] Controlled studies did not extend beyond 6 months.

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

No dosage adjustment is necessary for elderly patients or for patients with renal impairment.

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

Missed Dose

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

Administration

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

DEXILANT® should be swallowed whole with plenty of water.

- Alternatively, DEXILANT® capsules can be opened and administered as follows:
  Open capsule;
  Sprinkle intact granules on one tablespoon of applesauce;
  Swallow immediately. Granules should not be chewed.

OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

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.[2] The results are summarized in Table 3.

Table 3:Effect on 24-Hour Intragastric pH on Day 5 After Administration of DEXILANT® or Lansoprazole

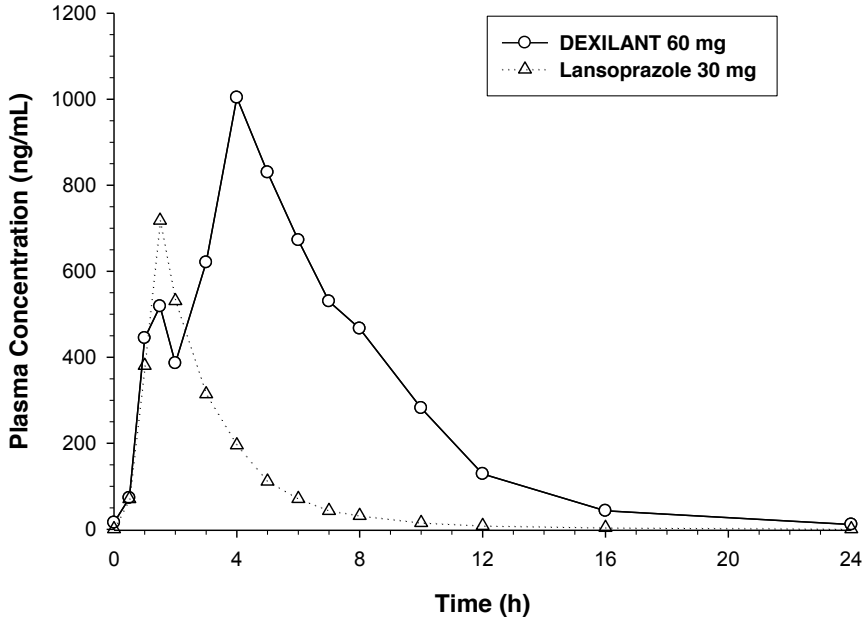
DEXILANT® 60 mg	Lansoprazole 30 mg
Mean Intragastric pH	
4.55*	4.13
% Time Intragastric pH > 4 (hours)	
71* (17 hours)	60 (14 hours)

* p value ≤0.05 versus lansoprazole.

Pharmacokinetics

The formulation of DEXILANT® utilizing Dual Delayed Release technology results in a dexlansoprazole plasma concentration-time profile with two distinct peaks; the first peak occurs 1 to 2 hours after administration, followed by a second peak within 4 to 5 hours (see Figure 1).[2,3]

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



Dexlansoprazole is eliminated with a half-life of approximately 1 to 2 hours in healthy subjects (see Table 4) and in patients with symptomatic GERD. No accumulation of dexlansoprazole occurs after multiple, once daily doses of DEXILANT® 30 mg or 60 mg.

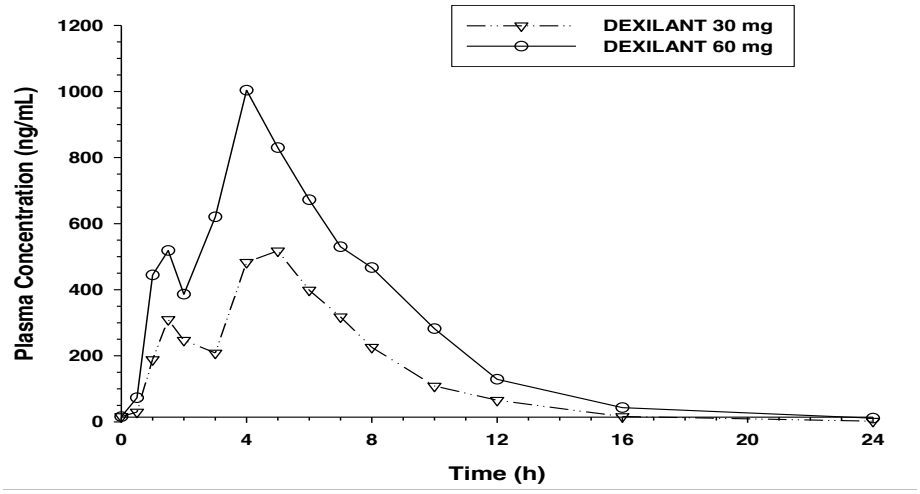
Table 4: Mean (CV %) Pharmacokinetic Parameters for Healthy Subjects on Day 5 After Administration of DEXILANT®

Dose (mg)	C_{max} (ng/mL)	AUC_{24} (ng·h/mL)	$t_{1/2}$[a] (h)	CL/F (L/h)	V_z/F
30	658 (40%) (N=44)	3275 (47%) (N=43)	1.49 (N=43)	11.4 (48%) (N=43)	25.7 (49%) (N=43)
60	1397 (51%) (N=79)	6529 (60%) (N=73)	1.54 (N=73)	11.6 (46%) (N=41)	33.8 (89%) (N=41)

[a] Harmonic mean

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

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



Distribution:
Plasma protein binding of dexlansoprazole ranged from 96.1% to 98.8% in healthy subjects and was independent of concentration from 0.01 to 20 mcg/mL. The apparent volume of distribution (Vz/F) after multiple doses in symptomatic GERD patients was 40.3 L.

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

CYP2C19 is a polymorphic liver enzyme which exhibits three phenotypes in the metabolism of CYP2C19 substrates; extensive metabolizers (*1/*1), intermediate metabolizers (*1/mutant) and poor metabolizers (mutant/mutant). Systemic exposure of dexlansoprazole is generally higher in intermediate and poor metabolizers. Dexlansoprazole is the major circulating component in plasma[4], 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/h, respectively, after 5-days of 30 or 60 mg once daily administration.

Effect of Food:
DEXILANT® can be taken without regard to food or the timing of food. In food-effect studies in healthy subjects receiving DEXILANT®, increases in C_{max} ranged from 12% to 55% and increases in AUC ranged from 9% to 37% under various fed conditions compared to fasting. However, no relevant differences with regard to intragastric pH were observed.[5] An additional study showed that administration of 60 mg DEXILANT® prior to consumption of breakfast, lunch, dinner or an evening snack did not have an effect on dexlansoprazole exposure, or a clinically relevant effect on 24-hour intragastric pH control.[6]

Special Populations and Conditions

Pediatrics:
The pharmacokinetics of dexlansoprazole in patients under the age of 18 years have not been studied.

Geriatrics:
In a study of 12 male and 12 female healthy subjects who received a single oral dose of DEXILANT® 60 mg, the terminal elimination half-life of dexlansoprazole was statistically significantly longer in geriatric subjects compared to younger subjects (2.23 and 1.5 hours, respectively). In addition, dexlansoprazole exhibited higher systemic exposure (AUC) in geriatric subjects (34.5% higher) than younger subjects. These differences were not clinically relevant. No dosage adjustment is necessary in geriatric patients (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Gender:
In a study of 12 male and 12 female healthy subjects who received a single oral dose of DEXILANT® 60 mg, females had higher systemic exposure (AUC) (42.8% higher) than males. No dosage adjustment is necessary in patients based on gender.

Hepatic Insufficiency:
In a study of 12 patients with moderately impaired hepatic function who received a single oral dose of DEXILANT® 60 mg, plasma exposure (AUC) of bound and unbound dexlansoprazole in the hepatic impairment group was approximately 2 times greater compared to subjects with normal hepatic function. This difference in exposure was not due to a difference in protein binding between the two liver function groups. No adjustment for DEXILANT® is necessary for patients with mild hepatic impairment (Child-Pugh Class A). DEXILANT® 30 mg should be considered for patients with moderate hepatic impairment (Child-Pugh Class B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C) (see **WARNINGS AND PRECAUTIONS**).

Renal Insufficiency:
Dexlansoprazole is extensively metabolized in the liver to inactive metabolites, and no parent drug is recovered in the urine following an oral dose of dexlansoprazole. Therefore, the pharmacokinetics of dexlansoprazole are not expected to be altered in patients with renal impairment, and no studies were conducted in subjects with renal impairment (see **WARNINGS AND PRECAUTIONS**).

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

DEXILANT® is supplied as a dual delayed release formulation in capsules for oral administration using Dual Delayed Release technology. The capsules contain dexlansoprazole in a mixture of two types of enteric-coated granules with different pH-dependent dissolution profiles. One type of granule is designed to release dexlansoprazole after the granules reach the proximal small intestine; the second type of granule is designed to release dexlansoprazole in the distal region of the small intestine, generally several hours later.

DEXILANT® is available in two dosage strengths: 30 mg and 60 mg, per capsule. Each capsule contains enteric-coated granules consisting of dexlansoprazole and the following non-medicinal ingredients: colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose 2910, low-substituted hydroxypropyl cellulose, magnesium carbonate, methacrylic acid copolymer, polyethylene glycol 8000, polysorbate 80, sucrose, sugar spheres, talc, titanium dioxide, and triethyl citrate.

The components of the capsule shell include the following non-medicinal ingredients: carrageenan, hypromellose and potassium chloride. Based on the capsule shell color, blue contains FD&C Blue No. 2 aluminum lake; gray contains black ferric oxide; and both contain titanium dioxide.

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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

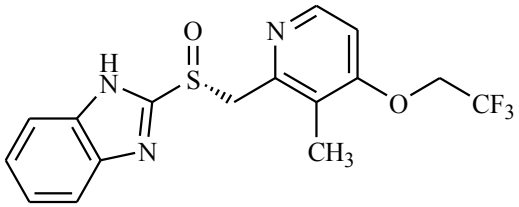
Drug Substance

Common name: Dexlansoprazole

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

Molecular formula and molecular mass: $C_{16}H_{14}F_3N_3O_2S$ 369.36

Structural formula:



Physicochemical properties:

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

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

CLINICAL TRIALS

Healing of Erosive Esophagitis

Two multi-center, double-blind, active-controlled, randomized, 8-week studies were conducted in patients with endoscopically confirmed erosive esophagitis.[7] Severity of the disease was classified based on the Los Angeles Classification Grading System (Grades A-D). Patients were randomized to one of the following three treatment groups: DEXILANT® 60 mg daily, DEXILANT® 90 mg daily or lansoprazole 30 mg daily. A total of 4092 patients were enrolled and ranged in age from 18 to 90 years (median age 48 years) with 54% male. Race was distributed as follows: 87% Caucasian, 5% Black and 8% other. Based on the Los Angeles Classification, 71% of patients had Grades A and B erosive esophagitis (mild) and 29% of patients had Grades C and D erosive esophagitis (moderate to severe) before treatment.

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

The crude rate estimates considered patients who did not have endoscopically documented healed erosive esophagitis and who discontinued prematurely as not healed. Based on crude rate estimates, healing rates at Week 4 (secondary) or Week 8 (primary) were higher for DEXILANT® than lansoprazole (Table 5). Treatment with DEXILANT® 60 mg was non-inferior to lansoprazole 30 mg at Week 8 in both studies. Statistical superiority of DEXILANT® 60 mg over lansoprazole 30 mg was established in the first study but was not replicated in the second study.

Table 5: Erosive Esophagitis Healing Rates – All Grades

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

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

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

The crude healing rates at Week 8 for patients with moderate to severe erosive esophagitis are presented in Table 6.

Table 6: Healing Rates at Week 8 – Moderate to Severe Erosive Esophagitis

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

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

* Statistically significant

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

Maintenance of Healed Erosive Esophagitis

A multi-center, double-blind, placebo-controlled, randomized study was conducted in patients who successfully completed a erosive esophagitis study and showed endoscopically confirmed healed erosive esophagitis.[8] Maintenance of healing and symptom relief over a six-month period were evaluated with DEXILANT® 30 mg or 60 mg once daily compared to placebo. A total of 445 patients were enrolled and ranged in age from 18 to 85 years (median age 49 years), with 52% female. Race was distributed as follows: 90% Caucasian, 5% Black and 5% other.

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

Based on crude rate estimates, 66.4% percent of patients treated with 30 mg or 60 mg of DEXILANT® remained healed over the six-month time period versus 14.3% of placebo patients ($p<0.00001$) (Table 7).

Table 7: Maintenance Rates[a] of Healed EE at Month 6

Number of Patients (N)[b]	Treatment Group (daily)	Maintenance Rate (%)
125	DEXILANT® 30 mg	66.4*
119	Placebo	14.3

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

[b] Patients with at least one post baseline endoscopy

* Statistically significant vs. placebo

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

DEXILANT® 30 mg and 60 mg achieved statistically significantly ($p<0.00001$) greater percentages of heartburn relief during the study treatment period. The median percentages of 24-hour heartburn-free days were 96.1%, 90.9% and 28.6% for DEXILANT® 30 mg, 60 mg and placebo, respectively. The median percentages of nights without heartburn were 98.9%, 96.2% and 71.7% for DEXILANT® 30 mg, 60 mg and placebo, respectively.

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

Symptomatic GERD

A multi-center, double-blind, placebo-controlled, randomized, 4-week study was conducted in patients with a diagnosis of symptomatic GERD made primarily by presentation of symptoms.[9] 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 and percent of nights without heartburn over placebo as assessed by daily diary over 4 weeks (Table 8). DEXILANT® 60 mg was studied and provided no additional clinical benefit over DEXILANT® 30 mg.

Table 8: Median Percentages of Heartburn Relief During the 4 Week Treatment Period of the Symptomatic GERD Study

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

* Statistically significant vs. placebo, $p<0.00001$

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

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics

Gastric Acid Secretion Effects in Rats and Dogs

Five studies compared the effect of dexlansoprazole on basal and stimulated gastric acid secretion in pylorus-ligated Sprague-Dawley (SD) male rats with those of lansoprazole. In all five studies, dexlansoprazole was more potent than lansoprazole in the suppression of gastric acid secretion. In studies of basal secretion, histamine 2HCl-, bethanechol chloride-, pentagastrin- and 2-deoxy-D-glucose-stimulated secretion, lansoprazole demonstrated potency values which were 63, 50, 83, 31 and 63%, respectively, of those seen with dexlansoprazole.

One study compared the effect of dexlansoprazole on histamine-stimulated gastric acid secretion in Heidenhain pouch male dogs with those of lansoprazole. Lansoprazole was less potent and demonstrated a potency value which was 45% of that seen with dexlansoprazole.

Effects on Alimentary Tract Injury in Rats

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

Pharmacokinetics

An *in situ* experiment was performed using surgically modified rats to explore the gastrointestinal sites of dexlansoprazole absorption. Five segments of the digestive tract (the stomach, the upper, middle and lower small intestine, and the large intestine) were isolated by ligation, and [^{14}C]dexlansoprazole was directly injected into the isolated segments. Blood samples were collected post-dose, and total radioactivity in the plasma was determined. Resulting plasma total radioactivity concentration-time curves were similar across all segments of the intestine, indicating similar absorption from each of the segments. In contrast, plasma total radioactivity concentrations in rats given an intragastric injection of [^{14}C]dexlansoprazole were very low. Together these results suggest that oral doses of dexlansoprazole were well absorbed from the small and large intestine of the rat, whereas relatively little was absorbed from the stomach.

Following the administration of [^{14}C]dexlansoprazole to pigmented (Long Evans) and non-pigmented (Sprague-Dawley) rats, [^{14}C]dexlansoprazole derived radioactivity was widely and rapidly distributed to most tissues and organs. Maximum concentrations of [^{14}C]dexlansoprazole derived radioactivity were obtained within 0.5 hour after dosing in nearly all tissues tested. In non-pigmented rats, the highest [^{14}C]dexlansoprazole derived radioactivity concentrations were found in the stomach, liver, intestine, thyroid and kidney. Total radioactivity

concentrations in all other tissues tested were generally similar to or less than those in plasma at the same time point. By 24 hours post dose, total radioactivity levels decreased to low levels in all tissues of the non–pigmented rats, with the exception of the thyroid which remained relatively high. In pigmented rats, radioactivity was generally preferentially distributed into organs of elimination. The tissues showing the highest concentrations of radioactivity, excluding the gastrointestinal tract, were liver, thyroid, renal cortex, urinary bladder, kidney, renal medulla, and uveal tract. Lingering radioactivity concentrations in the uveal tract suggests that [^{14}C]dexlansoprazole derived radioactivity binds to melanin.

Dexlansoprazole was metabolized to its inactive metabolites via oxidation, reduction, and subsequent formation of sulfate, glucuronide and glutathione conjugates. Dexlansoprazole was extensively metabolized by both rats and dogs, but some differences in metabolic patterns were observed between the species, most notably in the plasma and urine. Dexlansoprazole was a major component in both rat and dog plasma metabolic profiles at early time points. 5-Sulfonyloxy dexlansoprazole sulfide was a major component in the plasma of both male and female rats, as well as 4-glucuronyloxy dexlansoprazole sulfide in the male rats. In dog plasma, dexlansoprazole sulfone, 5-glucuronyloxy dexlansoprazole and 5-glucuronyloxy dexlansoprazole sulfone were the major metabolites. Glutathione-derived conjugates were the major metabolites in rat urine, whereas dexlansoprazole derived glucuronides and sulfates were the major metabolites in dog urine. 5-Hydroxy dexlansoprazole sulfide (M-IV) was the major component in fecal metabolic profiles, and dexlansoprazole derived glucuronides and sulfates accounted for the majority of the radioactive peaks in the biliary metabolic profiles from both rats and dogs.

Following administration of a [^{14}C]dexlansoprazole dose, fecal excretion was the main route of elimination in rats and dogs. Approximately 69% to 81% and 53% to 83% of the administered radioactive dose was recovered in the feces of rats and dogs, respectively. Biliary excretion of total radioactivity following oral administration of [^{14}C]dexlansoprazole to male and female bile duct cannulated rats and dogs averaged approximately 51% and 45 to 63% of the administered dose, respectively, within 96 hours post-dose. Dexlansoprazole derived glucuronides and sulfates accounted for the majority of the radioactivity excreted into the bile of both rats and dogs. Urinary recovery of [^{14}C]dexlansoprazole derived radioactivity ranged from approximately 15% to 25% in rats, and 13% to 30% in dogs. Glutathione-derived conjugates were the major metabolites in rat urine, whereas dexlansoprazole derived glucuronides and sulfates were the major metabolites in dog urine. No unchanged parent drug was measurable in the urine, feces or bile of rats or dogs.

Human Pharmacology

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 1025 patients for up to 6 to 12 months. The mean fasting gastrin concentrations increased from baseline during treatment with DEXILANT® 30 mg and 60 mg doses. In general, in patients treated for more than 6 months, mean serum gastrin levels increased during approximately the first 3 months of treatment and were stable for the remainder of treatment. Mean serum gastrin levels returned to pre-treatment levels within one month of discontinuation of treatment.

Enterochromaffin-Like Cell (ECL) Effects

There were no reports of ECL cell hyperplasia in gastric biopsy specimens obtained from 857 patients treated with DEXILANT® 30 mg, 60 mg or 90 mg for up to 12 months. See **TOXICOLOGY, Carcinogenicity.**

Effect on Cardiac Repolarization

A study was conducted to assess the potential of DEXILANT® to prolong the QT/QT_c interval in healthy adult subjects.[10] DEXILANT® doses of 90 mg or 300 mg did not delay cardiac repolarization compared to placebo. The positive control (moxifloxacin) produced statistically significantly greater mean maximum and time-averaged QT/QT_c intervals compared to placebo.

Effect of Co-administration with 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 coadministered compared to administration of clopidogrel alone.

Pharmacodynamic parameters were also measured and demonstrated that the change in inhibition of platelet aggregation (induced by 5 mcM ADP) was related to the change in the exposure to clopidogrel active metabolite. The clinical significance of this finding is not clear.

TOXICOLOGY

Multi-dose Studies

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

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

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

Carcinogenicity

Lansoprazole is a racemic mixture of R- and S-enantiomers. Following administration of lansoprazole in humans and animals, the major component circulating in plasma is dexlansoprazole, the R-enantiomer of lansoprazole.[4] Therefore, the carcinogenic potential of dexlansoprazole was assessed using existing lansoprazole studies. In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with lansoprazole at doses of 5 to 150 mg/kg/day, about 1 to 40 times the exposure on a body surface (mg/m^2) basis of a 50 kg person of average height (1.46 m^2 BSA) given the recommended human dose of lansoprazole of 30 mg/day (22.2 mg/m^2). Lansoprazole produced dose-related gastric ECL cell hyperplasia and ECL cell carcinoids in both male and female rats (see **DETAILED PHARMACOLOGY, Human 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/kg/day (4 to 40 times the recommended lansoprazole human dose based on BSA) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg lansoprazole/kg/day (13 times the recommended lansoprazole human dose based on BSA) in a 1-year toxicity study.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with lansoprazole doses of 15 mg to 600 mg/kg/day, 2 to 80 times the recommended human dose based on BSA. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. Lansoprazole also induced a low, non-dose-related incidence of carcinoid tumors in the gastric mucosa in several dose groups (one female mouse in the 15 mg/kg/day group, one male mouse in the 150 mg/kg/day group, and 2 males and 1 female in the 300 mg/kg/day group). It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 mg and 600 mg lansoprazole/kg/day (40 to 80 times the recommended lansoprazole human dose based on BSA) and female mice treated with 150 mg to 600 mg lansoprazole/kg/day (20 to 80 times the recommended human dose based on BSA) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg/kg/day (10 to 80 times the recommended lansoprazole human dose based on BSA).

Mutagenicity

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

Reproduction and Teratology

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

of dexlansoprazole and lansoprazole. The dexlansoprazole NOAEL for general toxicity in the dams was 3 mg/ kg/day. For reproductive toxicity, the NOAEL was greater than or equal to 30 mg/kg/day. For embryo-fetal development, the NOAEL was 10 mg/kg.

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

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PART III: CONSUMER INFORMATION
PrDEXILANT®
(dexlansoprazole) delayed release capsules

This leaflet is part III of a three-part "Product Monograph" published when DEXILANT® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DEXILANT®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT DEXILANT®

What the medication is used for:
DEXILANT® is used in adults to:

- help heal damage to the esophagus (throat) from erosive reflux esophagitis (acid backing up from the stomach which damages throat tissue).
- help maintain healed erosive esophagitis.
- relieve daytime and night time heartburn and other symptoms related to non-erosive gastroesophageal reflux disease (GERD) such as the burning, sour taste and burping.

What it does:
DEXILANT® is a medicine called a proton pump inhibitor (PPI).

DEXILANT® reduces the amount of acid in your stomach. When the stomach acid backs up (or refluxes) into your esophagus (throat) it burns and causes tissue damage as well as a sour taste and burping. By reducing the acid, DEXILANT® reduces these symptoms.

When you take DEXILANT®, some of the medicine is released in your body early and the rest is released several hours later, so the medicine continues to work.

When it should not be used:
You should not take DEXILANT® if you are allergic to DEXILANT® or any of its ingredients (*see* "What the non-medicinal ingredients are:"). DEXILANT® should not be taken with atazanavir.

What the medicinal ingredient is:
DEXILANT® contains dexlansoprazole as the active ingredient.

What the non-medicinal ingredients are:
Capsule granules: colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose 2910, low-substituted hydroxypropyl cellulose, magnesium carbonate, methacrylic acid copolymer, polyethylene glycol 8000, polysorbate 80, sucrose, sugar spheres, talc, titanium dioxide, and triethyl citrate.
Capsule shell: carrageenan, hypromellose, and potassium chloride.
Capsule shell color: blue contains FD&C Blue No.2 aluminum lake; gray contains black ferric oxide; and both contain titanium dioxide.

What dosage forms it comes in:
DEXILANT® is available in capsules containing 30 mg or 60 mg of dexlansoprazole.

WARNINGS AND PRECAUTIONS

BEFORE you use DEXILANT® talk to your doctor or pharmacist if:

- You are taking:
  - ampicillin
  - atazanavir
  - digoxin
  - iron salts
  - ketoconazole
  - warfarin
  - tacrolimus
  - theophylline
  - methotrexate
- You are taking any other medicines including non-prescription drugs, herbal products or supplements
- You have liver problems
- You have any allergies to this drug or its ingredients
- You are pregnant or could be pregnant
- You are breastfeeding
- You experience any cardiovascular (e.g. heart) or neurological (e.g. brain) symptoms including palpitations (rapid heartbeat), dizziness, seizures, and tetany (muscle condition with symptoms such as twitching, spasms, cramps and convulsions) as these may be signs of hypomagnesemia (low magnesium levels in the body)

DEXILANT® may stop your pain and other acid-related symptoms but you could still have serious stomach problems. Talk to your doctor.

Under rare circumstances, supervised by your doctor, proton pump inhibitors might be used for long periods. You should take DEXILANT®® exactly as prescribed, at the lowest dose possible for your treatment and for the shortest time needed.
People who take multiple daily doses of proton pump inhibitor medicines for a long period of time (a year or longer) may have an increased risk of fractures of the hip, wrist or spine. Talk to your doctor about your risk of bone fracture if you take DEXILANT®.
Long term use of proton pump inhibitors may prevent normal absorption of Vitamin B12 from the diet and could lead to Vitamin B12 deficiency. Talk to your doctor.

INTERACTIONS WITH DEXILANT®

Drugs that may interact with DEXILANT® include:

- ampicillin
- atazanavir
- digoxin
- iron salts
- ketoconazole
- warfarin
- tacrolimus
- theophylline
- methotrexate

PROPER USE OF DEXILANT®

Usual adult dose:
The recommended dose of DEXILANT® is not the same for all the indications.

If you have erosive esophagitis:
The recommended dose is 60 mg once daily for up to 8 weeks.
If you are on maintenance treatment for healed erosive esophagitis:
The recommended dose is 30 mg once daily for up to 6 months as directed by your doctor. Alternatively, your doctor may prescribe a 60 mg dose depending on your condition.

If you have heartburn related to non-erosive GERD:
The recommended dose is 30 mg once daily for 4 weeks.

Administration:
Take this medication exactly as it was prescribed and for the full length of time.

- You can take DEXILANT® with or without food.
- DEXILANT® should be swallowed whole with plenty of water.
- DEXILANT® capsules can be opened and the contents sprinkled on a tablespoon of applesauce. Swallow immediately. Granules should not be chewed.

Overdose:

In case of drug overdose, contact a healthcare practitioner (e.g. doctor), hospital emergency department or the regional Poison Control Centre, immediately even if there are no symptoms.

If you take more than the recommended dose of DEXILANT®, contact your doctor or the nearest regional Poison Control Centre.

Missed Dose:
If you miss a dose of DEXILANT®, take your DEXILANT® as soon as you remember. If it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Common side effects of DEXILANT® reported in clinical trials were constipation, diarrhea, gas, headache, nausea, and stomach pain.

Serious side effects from dexlansoprazole are not common.

After stopping your medication, your symptoms may get worse and your stomach may increase the acid production.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	*Clostridium difficile* colitis with symptoms such as severe (watery or bloody) diarrhea, fever, abdominal pain or tenderness			✓
	Liver problems (hepatitis or cholestasis with symptoms such as dark-coloured urine and pale stools, yellowing of skin and eyes (jaundice), stomach pain)		✓	
Rare	Convulsion or seizure			✓
Very rare	Serious allergic reactions (anaphylaxis), with symptoms such as severe rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing			✓
	Serious skin reactions, symptoms include widespread rash, itching, or hives, peeling of the skin, blisters on the skin, mouth, nose, eyes and genitals			✓

This is not a complete list of side effects. For any unexpected effects while taking DEXILANT®, contact your doctor or pharmacist.

HOW TO STORE DEXILANT®

Store DEXILANT® at room temperature, 15°-30°C.
Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to:**
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

    Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your healthcare professionals or pharmacist first, or Takeda Canada Inc. at 1-866-295-4636 or visit the website at www.takedacanada.com

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