DEXTOP
(Dexlansoprazole)

30mg & 60mg

Dual Delayed-Release Capsule

COMPOSITION

Each Capsule contains:
Dexlansoprazole…. 30mg (As dual delayed-release pellets)

Each Capsule contains:
Dexlansoprazole… 60mg (As dual delayed-release pellets)

THERAPEUTIC INDICATIONS

Healing of Erosive Esophagitis

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

Maintenance of Healed Erosive Esophagitis and Relief of Heartburn

Dexlansoprazole 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.

Treatment of Symptomatic Non-Erosive Gastroesophageal Reflux Disease

Dexlansoprazole 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

Table 1. Recommended Dexlansoprazole Capsules Dosage Regimen by Indication in Patients 12 Years of Age and Older

Indication	Dosage of Dexlansoprazole 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.

Dosage Adjustment in Patients with Hepatic Impairment for the Healing of Erosive Esophagitis

For patients with moderate hepatic impairment (Child-Pugh Class B), the recommended dosage is 30 mg Dexlansoprazole once daily for up to eight weeks. Dexlansoprazole is not recommended in patients with severe hepatic impairment (Child-Pugh Class C)

Method of administration

Take without regard to food.
Missed doses: If a dose is missed, administer as soon as possible. However, if the next scheduled dose is due, do not take the missed dose, and take the next dose on time. Do not take two doses at one time to make up for a missed dose.
Swallow whole; do not chew.
For patients who have trouble swallowing capsules, Dexlansoprazole capsules can be opened *For patients with swallowing difficulties and for children who can drink or swallow semi-solid food*
Patients can open the capsule and swallow the contents with half a glass of water or after mixing the contents in a slightly acidic fluid e.g., fruit juice or applesauce, or in non-carbonated water. Patients should be advised that the dispersion should be taken immediately (or within 30 minutes) and always be stirred just before drinking and rinsed down with half a glass of water.
Alternatively, patients can suck the capsule and swallow the pellets with half a glass of water. The enteric coated pellets must not be chewed.

CONTRAINDICATIONS

Dexlansoprazole is contraindicated in patients with known hypersensitivity to any component of the formulation. Hypersensitivity reactions, including anaphylaxis have been reported. Acute interstitial nephritis (AIN) has been reported with other proton pump inhibitors (PPIs), including lansoprazole of which Dexlansoprazole is the R-enantiomer

PPIs, including Dexlansoprazole, are contraindicated with rilpivirine-containing products

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Presence of Gastric Malignancy

In adults, symptomatic response to therapy with Dexlansoprazole 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.

Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including lansoprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue Dexlansoprazole if acute interstitial nephritis develops.

***Clostridium difficile*-Associated Diarrhea**

Published observational studies suggest that PPI therapy like Dexlansoprazole 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.

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

Bone Fracture

Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the conditions being treated.

Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines.

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 Dexlansoprazole, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in four to 12 weeks.

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

Cyanocobalamin (Vitamin B12) Deficiency

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

Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), healthcare professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

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.

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

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.

Tables below include drugs with clinically important drug interactions and interaction with diagnostics when administered concomitantly with Dexlansoprazole and instructions for preventing or managing them.

DRUG INTERACTIONS

Clinically Relevant Interactions Affecting Drugs Co-Administered with Dexlansoprazole 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 Dexlansoprazole is contraindicated Atazanavir: See prescribing information for atazanavir for dosing information. Nelfinavir: Avoid concomitant use with Dexlansoprazole. Saquinavir: monitor for potential saquinavir toxicities.
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.
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.
Intervention:	A temporary withdrawal of Dexlansoprazole 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.
Drugs Dependent on Gastric pH for Absorption (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate 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 Dexlansoprazole and MMF. Use Dexlansoprazole with caution in transplant patients receiving MMF
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.
Intervention:	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.
Interaction with Secretin Stimulation Test	
Clinical Impact:	Hyper-response in gastrin secretion in response to secretin stimulation test, falsely suggesting gastrinoma.
Intervention:	Temporarily stop Dexlansoprazole treatment at least 30 days before assessing to allow gastrin levels to return to baseline
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.

Clinically Relevant Interactions Affecting Dexlansoprazole When Co-Administered with Other Drugs and Substances	
CYP2C19 or CYP3A4 Inducers	
Clinical Impact:	Decreased exposure of Dexlansoprazole when used concomitantly with strong inducers.
Intervention:	St. John's Wort, rifampin: Avoid concomitant use with Dexlansoprazole
CYP2C19 or CYP3A4 Inhibitors	
Clinical Impact:	Increased exposure of Dexlansoprazole is expected when used concomitantly with strong inhibitors.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

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

Breast-feeding

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

EFFECTS ON ABILITY TO DRIVE

Dexlansoprazole is not likely to affect the ability to drive or use machines. Adverse drug reactions such as dizziness and visual disturbances may occur. If affected, patients should not drive or operate machinery.

ADVERSE DRUG REACTIONS

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

- Acute Interstitial Nephritis
- *Clostridium difficile*-Associated Diarrhea
- Bone Fracture
- Cutaneous and Systemic Lupus Erythematosus
- Cyanocobalamin (Vitamin B12) Deficiency
- Hypomagnesemia
- Fundic Gland Polyps

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.

Common Adverse Reactions

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

Table: Common Adverse Reactions in Controlled Studies in Adults

Adverse Reaction	**Placebo (N=896) %**	**Dexlansoprazole 30 mg (N=455) %**	**Dexlansoprazole 60 mg (N=2218) %**	**Dexlansoprazole 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 Dexlansoprazole 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

Post marketing Experience

The following adverse reactions have been identified during post-approval of Dexlansoprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura

Ear and Labyrinth Disorders: deafness

Eye Disorders: blurred vision

Gastrointestinal Disorders: oral edema, pancreatitis, fundic gland polyps
General Disorders and Administration Site Conditions: facial edema
Hepatobiliary Disorders: drug-induced hepatitis

Immune System Disorders: anaphylactic shock (requiring emergency intervention), exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal)

Infections and Infestations: Clostridium difficile-associated diarrhea
Metabolism and Nutrition Disorders: hypomagnesemia, hyponatremia
Musculoskeletal System Disorders: bone fracture

Nervous System Disorders: cerebrovascular accident, transient ischemic attack

Renal and Urinary Disorders: acute renal failure

Respiratory, Thoracic and Mediastinal Disorders: pharyngeal edema, throat tightness

Skin and Subcutaneous Tissue Disorders: generalized rash, leukocytoclastic vasculitis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com

OVERDOSE

There have been no reports of significant overdose with Dexlansoprazole Multiple doses of Dexlansoprazole 120 mg and a single dose of Dexlansoprazole 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 Dexlansoprazole 60 mg. Non-serious adverse reactions observed with twice daily doses of Dexlansoprazole 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Selective proton plump inhibitor, substituted benzimidazole.

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.

Pharmacodynamics

Antisecretory Activity

The effects of Dexlansoprazole 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 below.

Effect on 24 Hour Intragastric pH on Day 5 After Administration of Dexlansoprazole or Lansoprazole	
Dexlansoprazole 60 mg	**Lansoprazole 30 mg**
Mean Intragastric pH	
4.55	4.13
% Time Intragastric pH >4 (hours)	
71 (17 hours)	60 (14 hours)

Serum Gastrin Effects

The effect of dexlansoprazole on serum gastrin concentrations was evaluated in approximately 3460 patients in clinical trials up to eight weeks and in 1023 patients for up to six to 12 months. The mean fasting gastrin concentrations increased from baseline during treatment with 30 and 60 mg Dexlansoprazole. In patients treated for more than six months, mean serum gastrin levels increased during approximately the first three months of treatment and were stable for the remainder of treatment. Mean serum gastrin levels returned to pre-treatment levels within one month of discontinuation of treatment.

Increased gastrin causes enterochromaffin-like cell hyperplasia and increased serum CgA levels. The increased CgA levels may cause false positive results in diagnostic investigations for neuroendocrine tumors.

Enterochromaffin-Like Cell (ECL) Effects

There were no reports of ECL cell hyperplasia in gastric biopsy specimens obtained from 653 patients treated with Dexlansoprazole 30, 60, or 90 mg for up to 12 months.

During lifetime exposure of rats dosed daily with up to 150 mg/kg/day of lansoprazole, marked hypergastrinemia was observed followed by ECL cell proliferation and formation of carcinoid tumors, especially in female rats

Cardiac Electrophysiology

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

Pharmacokinetics

The dual delayed-release formulation of Dexlansoprazole results in a dexlansoprazole plasma concentration-time profile with two distinct peaks; the first peak occurs one to two hours after administration, followed by a second peak within four to five hours. Dexlansoprazole is eliminated with a half-life of approximately one to two hours in healthy subjects and in patients with symptomatic GERD. No accumulation of dexlansoprazole occurs after multiple, once daily doses of Dexlansoprazole 30 or 60 mg although mean AUCt and Cmax values of dexlansoprazole were slightly higher (less than 10%) on Day 5 than on Day 1.

The pharmacokinetics of dexlansoprazole are highly variable shown in table below, with percent coefficient of variation (%CV) values for Cmax, AUC, and CL/F of greater than 30%

Mean (%CV) Pharmacokinetic Parameters for Adult Subjects on Day 5 After Administration of Dexlansoprazole

Dose (mg)	**Cmax (ng/mL)**	**AUC24 (ng·h/mL)**	**CL/F (L/h)**
30	658 (40%) (N=44)	3275 (47%) (N=43)	11.4 (48%) (N=43)
60	1397 (51%) (N=79)	6529 (60%) (N=73)	11.6 (46%) (N=41)

Absorption

After oral administration of Dexlansoprazole 30 or 60 mg to healthy subjects and symptomatic GERD patients, mean Cmax and AUC values of dexlansoprazole increased approximately dose proportionally.

When granules of Dexlansoprazole 60 mg are mixed with water and dosed via NG tube or orally via syringe, the bioavailability (Cmax and AUC) of dexlansoprazole was similar to that when Dexlansoprazole 60 mg was administered as an intact capsule

Effect on Food

In food-effect studies in healthy subjects receiving Dexlansoprazole under various fed conditions compared to fasting, increases in Cmax ranged from 12 to 55%, increases in AUC ranged from 9 to 37%, and Tmax varied (ranging from a decrease of 0.7 hours to an increase of three hours)

Distribution

Plasma protein binding of dexlansoprazole ranged from 96 to 99% in healthy subjects and was independent of concentration from 0.01 to 20 mcg/mL. The apparent volume of distribution (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 Dexlansoprazole, no unchanged dexlansoprazole is excreted in urine. Following the administration of [^{14}C] dexlansoprazole to six healthy male subjects, approximately 50.7% (standard deviation (SD): 9.0%) of the administered radioactivity was excreted in urine and 47.6% (SD: 7.3%) in the feces.

Apparent clearance (CL/F) in healthy subjects was 11.4 to 11.6 L/hour, respectively, after five days of 30 or 60 mg once daily administration

Specific Populations

Age: 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 Dexlansoprazole *30 or 60 mg once daily for seven days. The dexlansoprazole mean Cmax 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*

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.

Sex

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

Renal Impairment

Dexlansoprazole is extensively metabolized in the liver to inactive metabolites, and no parent drug is recovered in the urine following an oral dose of dexlansoprazole. Therefore, the pharmacokinetics of dexlansoprazole are not expected to be altered in patients with renal impairment, and no studies were conducted in patients with renal impairment. In addition, the pharmacokinetics of lansoprazole were not

clinically different in patients with mild, moderate or severe renal impairment compared to healthy subjects with normal renal function.

Hepatic Impairment

In a study of 12 patients with moderate hepatic impairment (Child-Pugh Class B) who received a single dose of 60 mg Dexlansoprazole, the systemic exposure (AUC) of bound and unbound dexlansoprazole was approximately two times greater compared to subjects with normal hepatic function. This difference in exposure was not due to a difference in protein binding. No studies have been conducted in patients with severe hepatic impairment.

Drug-Drug Interactions

Effect of Dexlansoprazole on Other Drugs

Cytochrome P 450 Interactions

Dexlansoprazole is metabolized, in part, by CYP2C19 and CYP3A4.

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 Dexlansoprazole 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 Dexlansoprazole 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 DEXLANSOPRAZOLE 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 DEXLANSOPRAZOLE 60 mg (n=40), for nine days was conducted. The mean AUC of the active metabolite of clopidogrel was reduced by approximately 9% (mean AUC ratio was 91%, with 90% CI of 86 to 97%) when DEXLANSOPRAZOLE was co-administered compared to administration of clopidogrel alone.

Pharmacodynamic parameters were also measured and demonstrated that the change in inhibition of platelet aggregation (induced by 5 mcM ADP) was related to the change in the exposure to clopidogrel active metabolite. The effect on exposure to the active metabolite of clopidogrel and on clopidogrel-induced platelet inhibition is not considered clinically important.

Effect of Other Drugs on Dexlansoprazole

Because dexlansoprazole is metabolized by CYP2C19 and CYP3A4, inducers and inhibitors of these enzymes may potentially alter exposure of dexlansoprazole.

Summary of Clinical Studies

Healing of Erosive Esophagitis in Adults

Two multi-center, double-blind, active-controlled, randomized, eight week studies were conducted in patients with endoscopically confirmed EE. Severity of the disease was classified based on the Los Angeles Classification Grading System (Grades A-D). Patients were randomized to one of the following three treatment groups: DEXLANSOPRAZOLE 60 mg once daily, DEXLANSOPRAZOLE 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

EE Healing Rates* in Adults: All Grades

Study	Number of Patients (N)†	Treatment Group (daily)	Week 4 % Healed	Week 8‡ % Healed	(95% CI) for the Treatment Difference (DEXLANSOPRAZOLE– Lansoprazole) by Week 8
1	657	DEXLANSOPRAZOLE 60 mg	70	87	(-1.5, 6.1)§
	648	Lansoprazole 30 mg	65	85	
2	639	DEXLANSOPRAZOLE 60 mg	66	85	(2.2, 10.5)§
	656	Lansoprazole 30 mg	65	79	

CI = Confidence interval

* Based on crude rate estimates, patients who did not have endoscopically documented healed EE and prematurely discontinued were considered not healed.

† Patients with at least one post-baseline endoscopy.

‡ Primary efficacy endpoint.

§ Demonstrated non-inferiority to lansoprazole.

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. Maintenance of healing and symptom resolution over a six month period was evaluated with Dexlansoprazole 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 Dexlansoprazole remained healed over the six month time period as confirmed by endoscopy

Maintenance Rates* of Healed EE at Month 6 in Adults

Number of Patients (N)†	Treatment Group (daily)	Maintenance Rate (%)
125	Dexlansoprazole 30 mg	66.4‡
119	Placebo	14.3

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

† Patients with at least one post-baseline endoscopy

‡ Statistically significant vs placebo

The effect of Dexlansoprazole 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. Dexlansoprazole 30 mg demonstrated a statistically significantly higher percent of 24 hour heartburn-free periods compared to placebo over the six month treatment period. The majority of patients treated with placebo discontinued due to relapse of EE between Month 2 and Month 6.

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

	Overall Treatment*		Month 1		Month 6	
Treatment Group (daily)	N	Heartburn-Free 24 hour Periods (%)	N	Heartburn- Free 24 hour Periods (%)	N	Heartburn- Free 24 hour Periods (%)
DEXLANSOPRAZOLE 30 mg	132	96.1†	126	96.7	80	98.3
Placebo	141	28.6	117	28.6	23	73.3

* Secondary efficacy endpoint

† Statistically significant vs placebo

Treatment of Symptomatic Non-Erosive GERD in Adults

A multi-center, double-blind, placebo-controlled, randomized, four week study was conducted in patients with a diagnosis of symptomatic non-erosive GERD made primarily by presentation of symptoms. These patients who identified heartburn as their primary symptom, had a history of heartburn for six months or longer, had heartburn on at least four of seven days immediately prior to randomization and had no esophageal erosions as confirmed by endoscopy. However, patients with symptoms which were not acid-related may not have been excluded using these inclusion criteria. Patients were randomized to one of the following treatment groups: Dexlansoprazole 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.

Dexlansoprazole 30 mg provided statistically significantly greater percent of days with heartburn-free 24 hour periods over placebo as assessed by daily diary over four weeks. Dexlansoprazole 60 mg once daily was studied and provided no additional clinical benefit over Dexlansoprazole 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	Dexlansoprazole 30 mg	54.9*
310	Placebo	18.5

* Statistically significant vs placebo

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

Pediatric GERD

Use of Dexlansoprazole in patients 12 to 17 years of age is supported by evidence from adequate and well- controlled studies of Dexlansoprazole 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 eight weeks, 62 patients were treated with Dexlansoprazole 60 mg once daily to evaluate the healing of EE. Of the 62 patients, 58 patients completed the eight week trial, and 51 (88%) patients achieved healing of EE, as confirmed by endoscopy, over eight weeks of treatment

Healing of EE at Week 8 in Pediatric Patients 12 to 17 Years of Age

	Dexlansoprazole 60 mg
Proportion of randomized patients healed	
n (%)	51/62 (82%)
95% CI	(70, 91)†
Proportion of evaluable patients healed*	
n (%)	51/58 (88%)
95% CI	(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 Dexlansoprazole 30 mg or placebo, once daily for an additional 16 weeks to evaluate maintenance of healing and symptom resolution. Maintenance of healing was assessed by endoscopy at Week 24. Of the 51 patients randomized, 13 patients discontinued early. Of these, five patients did not undergo post-baseline endoscopy. Eighteen of 22 (82%) evaluable patients treated with Dexlansoprazole 30 mg remained healed over the 16 week treatment period as confirmed by endoscopy, compared with 14 of 24 (58%) in placebo shown in table below

Maintenance of Healed EE at Week 24* in Pediatric Patients 12 to 17 Years of Age

	Dexlansoprazole 30 mg	Placebo
Proportion of randomized patients who maintained healing of EE		
n (%)	18/25 (72%)	14/26 (54%)
95% CI	(51, 88)‡	(33, 73)‡

Proportion of evaluable patients who maintained healing of EE†		
n (%)	18/22 (82%)	14/24 (58%)
95% CI	(60, 95)‡	(37, 78)‡

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

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

‡ Reported are the exact confidence limits.

Relief of heartburn was assessed in randomized patients during the 16 week maintenance period. The median percentage of 24 hour heartburn-free periods was 87% for those receiving Dexlansoprazole 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 Dexlansoprazole 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 Dexlansoprazole 30 mg once daily, for four 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 three out of seven days during screening, and had no esophageal erosions as confirmed by endoscopy. The median age was 15 years, with females accounting for 70% of the patients. During the four week treatment period, the median percentage of 24 hour heartburn free periods was 47%.

Maintenance of Healed EE at Week 24* in Pediatric Patients 12 to 17 Years of Age

	Dexlansoprazole 30 mg	Placebo
Proportion of randomized patients who maintained healing of EE		
n (%)	18/25 (72%)	14/26 (54%)
95% CI	(51, 88)‡	(33, 73)‡
Proportion of evaluable patients who maintained healing of EE†		
n (%)	18/22 (82%)	14/24 (58%)
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* Following eight weeks of initial therapy and 16 weeks of maintenance therapy.

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PRECLINICAL SAFETY DATA

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of dexlansoprazole was assessed using lansoprazole studies. In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with lansoprazole at doses of 5 to

150 mg/kg/day, about one to 40 times the exposure on a body surface (mg/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/day.

Lansoprazole produced dose-related gastric ECL cell hyperplasia and ECL cell carcinoids in both male and female rats.

In rats, lansoprazole also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg/kg/day (four to 40 times the recommended human lansoprazole dose based on BSA) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat.

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

A 26 week p53 (+/-) transgenic mouse carcinogenicity study of lansoprazole was not positive.

Lansoprazole was positive in the Ames test and the *in vitro* human lymphocyte chromosomal aberration assay. Lansoprazole was not genotoxic in the *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) test, the *in vivo* mouse micronucleus test or the rat bone marrow cell chromosomal aberration test.

Dexlansoprazole was positive in the Ames test and in the *in vitro* chromosome aberration test using Chinese hamster lung cells. Dexlansoprazole was negative in the *in vivo* mouse micronucleus test.

The potential effects of dexlansoprazole on fertility and reproductive performance were assessed using lansoprazole studies. Lansoprazole at oral doses up to 150 mg/kg/day (40 times the recommended human lansoprazole dose based on BSA) was found to have no effect on fertility and reproductive performance of male and female rats.

PRESENTATION

Dextop 30mg capsules are available in pack of 3x10's alu alu blister.

Dextop 60mg capsules are available in pack of 3x10's alu alu blister.

INSTRUCTIONS

- To be sold on the prescription of a registered medical practitioner only.
- Protect from heat, sunlight & moisture.
- Store below 30°C.
- Keep all medicines out of the reach of children.
-

REGISTRATION NUMBER

Dextop 30mg Capsules: 086978

Dextop 60mg Capsules: 086979

Manufacturing License No: 000016

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Manufactured by:

The Searle Company Limited,

F-319, S.I.T.E., Karachi-Pakistan.

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