

# **CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**22-287**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KAPIDEX safely and effectively. See full prescribing information for KAPIDEX.

**KAPIDEX (dexlansoprazole) delayed release capsules**  
Initial U.S. Approval: 1995 (lansoprazole)

### INDICATIONS AND USAGE

KAPIDEX is a proton pump inhibitor (PPI) indicated for:

- Healing of all grades of erosive esophagitis (EE). (1.1)
- Maintaining healing of EE. (1.2)
- Treating heartburn associated with non-erosive gastroesophageal reflux disease (GERD). (1.3)

### DOSAGE AND ADMINISTRATION

- Healing of EE: 60 mg once daily for up to 8 weeks. (2.1)
- Maintenance of healed EE: 30 mg once daily for up to 6 months. (2.1)
- Symptomatic non-erosive GERD: 30 mg once daily for 4 weeks. (2.1)
- Hepatic impairment: Consider 30 mg maximum daily dose for patients with moderate hepatic impairment (Child-Pugh Class B). No studies were conducted in patients with severe hepatic impairment (Child-Pugh Class C). (2.2, 8.7)
- KAPIDEX can be taken without regard to food. (2.3)
- KAPIDEX should be swallowed whole. Alternatively, capsules can be opened, sprinkled on one tablespoon of applesauce, and swallowed immediately. (2.3)

### DOSAGE FORMS AND STRENGTHS

Capsules: 30 mg and 60 mg. (3)

### CONTRAINDICATIONS

Patients with known hypersensitivity to any component of the formulation. (4)

### WARNINGS AND PRECAUTIONS

Gastric malignancy: Symptomatic response with KAPIDEX does not preclude the presence of gastric malignancy. (5.1)

### ADVERSE REACTIONS

Most commonly reported adverse reactions ( $\geq 2\%$ ): diarrhea, abdominal pain, nausea, upper respiratory tract infection, vomiting, and flatulence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals America, Inc. at 1.877.825.3326 or FDA at 1.800.FDA.1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Atazanavir: Do not co-administer with KAPIDEX because atazanavir systemic concentrations may be substantially decreased. (7.1)
- Drugs with pH-dependent absorption (e.g., ampicillin esters, digoxin, iron salts, ketoconazole): KAPIDEX may interfere with absorption of drugs for which gastric pH is important for bioavailability. (7.1)
- Warfarin: Patients taking concomitant warfarin may require monitoring for increases in international normalized ratio (INR) and prothrombin time. (7.2)

### USE IN SPECIFIC POPULATIONS

- Nursing mothers: Discontinue drug or nursing, taking into consideration importance of drug to mother. (8.4)
- Pediatric use: Safety and effectiveness not established in pediatric patients. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling.

Revised: 1/2009

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## ULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Healing of Erosive Esophagitis

KAPIDEX is indicated for healing of all grades of erosive esophagitis (EE) for up to 8 weeks.

#### 1.2 Maintenance of Healed Erosive Esophagitis

KAPIDEX is indicated to maintain healing of EE for up to 6 months.

#### 1.3 Symptomatic Non-Erosive Gastroesophageal Reflux Disease

KAPIDEX is indicated for the treatment of heartburn associated with non-erosive gastroesophageal reflux disease (GERD) for 4 weeks.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dose

KAPIDEX is available as capsules in 30 mg and 60 mg strengths for adult use. Directions for use in each indication are summarized in Table 1.

Table 1: KAPIDEX Dosing Recommendations

| Indication                   | Recommended Dose | Frequency                    |
|------------------------------|------------------|------------------------------|
| Healing of EE                | 60 mg            | Once daily for up to 8 weeks |
| Maintenance of Healed EE     | 30 mg            | Once daily*                  |
| Symptomatic Non-Erosive GERD | 30 mg            | Once daily for 4 weeks       |

\*Controlled studies did not extend beyond 6 months.

#### 2.2 Special Populations

No adjustment for KAPIDEX is necessary for patients with mild hepatic impairment (Child-Pugh Class A). Consider a maximum daily dose of 30 mg 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 *Use in Specific Populations* (8.7) and *Clinical Pharmacology* (12.5)].

No dosage adjustment is necessary for elderly patients or for patients with renal impairment [see *Clinical Pharmacology* (12.5)].

#### 2.3 Important Administration Information

KAPIDEX can be taken without regard to food.

KAPIDEX should be swallowed whole.

- Alternatively, KAPIDEX capsules can be opened and administered as follows:
  - Open capsule;
  - Sprinkle intact granules on one tablespoon of applesauce;
  - Swallow immediately.

### 3 DOSAGE FORMS AND STRENGTHS

- 30 mg capsules are opaque, blue and gray with TAP and "30" imprinted on the capsule.
- 60 mg capsules are opaque, blue with TAP and "60" imprinted on the capsule.

### 4 CONTRAINDICATIONS

KAPIDEX is contraindicated in patients with known hypersensitivity to any component of the formulation [see *Description* (11)]. Hypersensitivity and anaphylaxis have been reported with KAPIDEX use [see *Adverse Reactions* (6.1)].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Gastric Malignancy

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

### 6 ADVERSE REACTIONS

#### 6.1 Clinical Trials Experience

The safety of KAPIDEX was evaluated in 4548 patients in controlled and uncontrolled clinical studies, including 863 patients treated for at least 6 months and 203 patients treated for one year. Patients ranged in age from 18 to 90 years (median age 48 years), with 54% female, 85% Caucasian, 8% Black, 4% Asian, and 3% other races. Six randomized controlled clinical trials were conducted for the treatment of EE, maintenance of healed EE, and symptomatic GERD, which included 896 patients on placebo, 455 patients on KAPIDEX 30 mg, 2218 patients on KAPIDEX 60 mg, and 1363 patients on lansoprazole 30 mg once daily.

As 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.

#### Most Commonly Reported Adverse Reactions

The most common adverse reactions ( $\geq 2\%$ ) that occurred at a higher incidence for KAPIDEX than placebo in the controlled studies are presented in Table 2.

**Table 2: Incidence of Treatment-Emergent Adverse Reactions  
in Controlled Studies**

| Adverse Reaction                  | Placebo<br>(N=896)<br>% | KAPIDEX<br>30 mg<br>(N=455)<br>% | KAPIDEX<br>60 mg<br>(N=2218)<br>% | KAPIDEX<br>Total<br>(N=2621)<br>% | Lansoprazole<br>30 mg<br>(N=1363)<br>% |
|-----------------------------------|-------------------------|----------------------------------|-----------------------------------|-----------------------------------|--|
| 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 KAPIDEX therapy was diarrhea (0.7%).

#### Other 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, nematochezia, hemorrhoids, impaired gastric emptying, irritable bowel syndrome, mucus stools, nausea and vomiting, oral mucosal blistering, painful defecation, proctitis, paresthesia oral, rectal hemorrhage

*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, pruritis, rash, skin lesion, urticaria

*Vascular Disorders:* deep vein thrombosis, hot flush, hypertension

Additional adverse reactions that were reported in a long-term uncontrolled study and were considered related to KAPIDEX by the treating physician included: anaphylaxis, auditory hallucination, B-cell lymphoma, central obesity, cholecystitis acute, decreased hemoglobin, dehydration, diabetes mellitus, dysphonia, epistaxis, folliculitis, gastrointestinal pain, gout, herpes zoster, hyperglycemia, hyperlipidemia, hypothyroidism, increased neutrophils, MCHC decrease, neutropenia, oral soft tissue disorder, rectal tenesmus, restless legs syndrome, somnolence, thrombocytopenia, tonsillitis.

Other adverse reactions not observed with KAPIDEX, but occurring with the racemate lansoprazole can be found in the lansoprazole package insert, ADVERSE REACTIONS section.

## 7 DRUG INTERACTIONS

### 7.1 Drugs with pH-Dependent Absorption Pharmacokinetics

KAPIDEX causes inhibition of gastric acid secretion. KAPIDEX 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, KAPIDEX should not be co-administered with atazanavir.

It is theoretically possible that KAPIDEX 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).

### 7.2 Warfarin

Co-administration of KAPIDEX 90 mg and warfarin 25 mg did not affect the pharmacokinetics of warfarin or INR [see *Clinical Pharmacology* (12.6)]. However, there have been reports of 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. Patients treated with KAPIDEX and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Teratogenic Effects

Pregnancy Category B. There are no adequate and well-controlled studies with dexlansoprazole in pregnant women. There were no adverse fetal effects in animal reproduction studies of dexlansoprazole in rabbits. Because animal reproduction studies are not always predictive of human response, KAPIDEX should be used during pregnancy only if clearly needed.

A reproduction study conducted in rabbits at oral dexlansoprazole doses up to 30 mg per kg per day (approximately 9-fold the maximum recommended human dexlansoprazole dose [60 mg] based on body surface area [BSA]) revealed no evidence of harm to the fetus due to dexlansoprazole. In addition, reproduction studies performed in pregnant rats with oral lansoprazole at doses up to 150 mg per kg per day (40 times the recommended human dose based on BSA) and in pregnant rabbits at oral lansoprazole doses up to 30 mg per kg per day (16 times the recommended human dose based on BSA) revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

### 8.3 Nursing Mothers

It is not known whether dexlansoprazole is excreted in human milk. However, lansoprazole and its metabolites are present in rat milk following the administration of lansoprazole. As many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies [see *Carcinogenesis, Mutagenesis, Impairment of Fertility* (13.1)], a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### 8.4 Pediatric Use

Safety and effectiveness of KAPIDEX in pediatric patients (less than 18 years of age) have not been established.

### 8.5 Geriatric Use

In clinical studies of KAPIDEX, 11% of patients were aged 65 years and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified significant differences in responses between geriatric and younger patients, but greater sensitivity of some older individuals cannot be ruled out [see *Clinical Pharmacology* (12.5)].

### 8.6 Renal Impairment

No dosage adjustment of KAPIDEX is necessary in patients with renal impairment. The pharmacokinetics of dexlansoprazole in patients with renal impairment are not expected to be altered since 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 [see *Clinical Pharmacology* (12.5)].

### 8.7 Hepatic Impairment

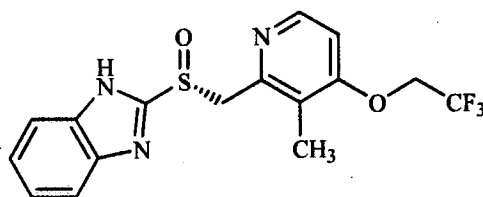
No dosage adjustment for KAPIDEX is necessary for patients with mild hepatic impairment (Child-Pugh Class A). KAPIDEX 30 mg should be considered for patients with moderate hepatic impairment (Child-Pugh Class B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C) [see *Clinical Pharmacology* (12.5)].

## 10 OVERDOSAGE

There have been no reports of significant overdose of KAPIDEX. Multiple doses of KAPIDEX 120 mg and a single dose of KAPIDEX 300 mg did not result in death or other severe adverse events. Dexlansoprazole is not expected to be removed from the circulation by hemodialysis. If an overdose occurs, treatment should be symptomatic and supportive.

## 11 DESCRIPTION

The active ingredient in KAPIDEX (dexlansoprazole) delayed release capsules is (+)-2-[(R)-[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulfanyl]-1H-benzimidazole, a compound that inhibits gastric acid secretion. Dexlansoprazole is the R-enantiomer of lansoprazole (a racemic mixture of the R- and S-enantiomers). Its empirical formula is: C<sub>16</sub>H<sub>14</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>S, with a molecular weight of 369.36. The structural formula is:



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

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

KAPIDEX is supplied as a dual delayed release formulation in capsules for oral administration. The capsules contain dexlansoprazole in a mixture of two types of enteric-coated granules with different pH-dependent dissolution profiles [see *Clinical Pharmacology* (12.3)].

KAPIDEX is available in two dosage strengths: 30 mg and 60 mg, per capsule. Each capsule contains enteric-coated granules consisting of dexlansoprazole (active ingredient) and the following inactive ingredients: sugar spheres, magnesium carbonate, sucrose, low-substituted hydroxypropyl cellulose, titanium dioxide, hydroxypropyl cellulose, hypromellose 2910, talc, methacrylic acid copolymer, polyethylene glycol 8000, triethyl citrate, polysorbate 80, and colloidal silicon dioxide. The components of the capsule shell include the following inactive ingredients: hypromellose, carrageenan and potassium chloride. Based on the capsule shell color, blue contains FD&C Blue No. 2 and aluminum lake; gray contains ferric oxide and aluminum lake; and both contain titanium dioxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Dexlansoprazole is a PPI that suppresses gastric acid secretion by specific inhibition of the (H<sup>+</sup>,K<sup>+</sup>)-ATPase in the gastric parietal cell. By acting specifically on the proton pump, dexlansoprazole blocks the final step of acid production.

### 12.2 Pharmacodynamics

#### Antisecretory Activity

The effects of KAPIDEX 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 3.

**Table 3: Effect on 24-hour Intragastric pH on Day 5 After Administration of KAPIDEX or Lansoprazole**

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

#### Serum Gastrin Effects

The effect of KAPIDEX on serum gastrin concentrations was evaluated in approximately 3460 patients in clinical trials up to 8 weeks and in 1023 patients for up to 6 to 12 months. The mean fasting gastrin concentrations increased from baseline during treatment with KAPIDEX 30 mg and 60 mg doses. 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 653 patients treated with KAPIDEX 30 mg, 60 mg or 90 mg for up to 12 months.

During lifetime exposure of rats dosed daily with up to 150 mg per kg per day of lansoprazole, marked hypergastrinemia was observed followed by ECL cell proliferation and formation of carcinoid tumors, especially in female rats [see *Nonclinical Toxicology* (13.1)].

#### Effect on Cardiac Repolarization

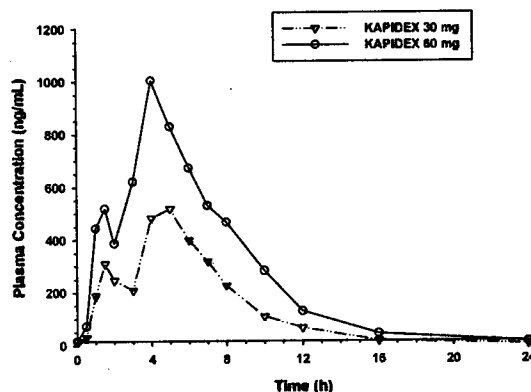
A study was conducted to assess the potential of KAPIDEX to prolong the QT/QT<sub>c</sub> interval in healthy adult subjects. KAPIDEX doses of 90 mg or 300 mg did not delay cardiac repolarization compared to placebo. The positive control (moxifloxacin) produced statistically significantly greater mean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

### 12.3 Pharmacokinetics

The dual delayed release formulation of KAPIDEX results in a dexlansoprazole plasma concentration-time profile with two distinct peaks; the first peak occurs 1 to 2 hours after administration, followed by a second peak within 4 to 5 hours ( see Figure 1). Dexlansoprazole is eliminated with a half-life of approximately 1 to 2 hours in healthy subjects and in patients with symptomatic GERD. No accumulation of dexlansoprazole occurs after multiple, once

aily doses of KAPIDEX 30 mg or 60 mg, although mean AUC<sub>t</sub> and C<sub>max</sub> values of dexlansoprazole were slightly higher (less than 10%) on day 5 than on day 1.

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



The pharmacokinetics of dexlansoprazole are highly variable, with percent coefficient of variation (CV%) values for C<sub>max</sub>, AUC, and CL/F of greater than 30% (see Table 4).

**Table 4: Mean (CV%) Pharmacokinetic Parameters for Subjects on Day 5 After Administration of KAPIDEX**

| Dose (mg) | C <sub>max</sub> (ng/mL) | AUC <sub>24</sub> (ng·h/mL) | CL/F (L/h)           |
|-----------|--------------------------|-----------------------------|----------------------|
| 30        | 658 (40%)<br>(N=44)      | 3275 (47%)<br>(N=43)        | 11.4 (48%)<br>(N=43) |
| 60        | 1397 (51%)<br>(N=79)     | 6529 (60%)<br>(N=73)        | 11.6 (46%)<br>(N=41) |

#### Absorption

After oral administration of KAPIDEX 30 mg or 60 mg to healthy subjects and symptomatic GERD patients, mean C<sub>max</sub> and AUC values of dexlansoprazole increased approximately dose proportionally (see Figure 1).

#### 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 per mL. The apparent volume of distribution (V<sub>d</sub>/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). Dexlansoprazole is the major circulating component in plasma regardless of CYP2C19 metabolizer status. In CYP2C19 intermediate and extensive metabolizers, the major plasma metabolites are 5-hydroxy dexlansoprazole and its glucuronide conjugate, while in CYP2C19 poor metabolizers dexlansoprazole sulfone is the major plasma metabolite.

#### Elimination

Following the administration of KAPIDEX, no unchanged dexlansoprazole is excreted in urine. Following the administration of [<sup>14</sup>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 CYP2C19 Polymorphism on Systemic Exposure of Dexlansoprazole

Systemic exposure of dexlansoprazole is generally higher in intermediate and poor metabolizers. In male Japanese subjects who received a single dose of KAPIDEX 30 mg or 60 mg (N=2 to 6 subjects/group), mean dexlansoprazole C<sub>max</sub> and AUC values were up to 2 times higher in intermediate compared to extensive metabolizers; in poor metabolizers, mean C<sub>max</sub> was up to 4 times higher and mean AUC was up to 12 times higher compared to extensive metabolizers. Though such study was not conducted in Caucasians and African Americans, it is expected dexlansoprazole exposure in these races will be affected by CYP2C19 phenotypes as well.

## 12.4 Effect of Food on Pharmacokinetics and Pharmacodynamics

In food-effect studies in healthy subjects receiving KAPIDEX under various fed conditions compared to fasting, increases in  $C_{max}$  ranged from 12% to 55%, increases in AUC ranged from 9% to 37%, and  $t_{max}$  varied (ranging from a decrease of 0.7 hours to an increase of 3 hours). No significant differences in mean intragastric pH were observed between fasted and various fed conditions. However, the percentage of time intragastric pH exceeded 4 over the 24-hour dosing interval decreased slightly when KAPIDEX was administered after a meal (57%) relative to fasting (64%), primarily due to a decreased response in intragastric pH during the first 4 hours after dosing. Because of this, while KAPIDEX can be taken without regard to food, some patients may benefit from administering the dose prior to a meal if post-meal symptoms do not resolve under post-fed conditions.

## 12.5 Special Populations

### Pediatric Use

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

### Geriatric Use

The terminal elimination half-life of dexlansoprazole is significantly increased in geriatric subjects compared to younger subjects (2.23 and 1.5 hours, respectively); this difference is not clinically relevant. Dexlansoprazole exhibited higher systemic exposure (AUC) in geriatric subjects (34.5% higher) than younger subjects. No dosage adjustment is needed in geriatric patients [see *Use in Specific Populations* (8.5)].

### 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 subjects with renal impairment [see *Use in Specific Populations* (8.6)]. In addition, the pharmacokinetics of lansoprazole were studied in patients with mild, moderate or severe renal impairment; results demonstrated no need for a dose adjustment for this patient population.

### Hepatic Impairment

In a study of 12 patients with moderately impaired hepatic function who received a single oral dose of KAPIDEX 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 KAPIDEX is necessary for patients with mild hepatic impairment (Child-Pugh Class A). KAPIDEX 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 *Use in Specific Populations* (8.7)].

### Gender

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

## 12.6 Drug-Drug Interactions

### Warfarin

In a study of 20 healthy subjects, co-administration of KAPIDEX 90 mg once daily for 11 days with a single 25 mg oral dose of warfarin on day 6 did not result in any significant differences in the pharmacokinetics of warfarin or INR compared to administration of warfarin with placebo. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly [see *Drug Interactions* (7.2)].

### Cytochrome P.450 Interactions

Dexlansoprazole is metabolized, in part, by CYP2C19 and CYP3A4 [see *Clinical Pharmacology* (12.3)].

In vitro studies have shown that KAPIDEX is not likely to inhibit CYP isoforms 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4. As such, no clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Furthermore, clinical drug-drug interaction studies in mainly CYP2C19 extensive and intermediate metabolizers have shown that KAPIDEX does not affect the pharmacokinetics of diazepam, phenytoin, or theophylline. The subjects' CYP1A2 genotypes in the drug-drug interaction study with theophylline were not determined.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of dexlansoprazole was assessed using lansoprazole studies. In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with lansoprazole at doses of 5 to 150 mg per kg per day, about 1 to 40 times the exposure on a body surface ( $\text{mg}/\text{m}^2$ ) basis of a 50 kg person of average height ( $1.46 \text{ m}^2$  BSA) given the recommended human dose of lansoprazole (30 mg per day).

Lansoprazole produced dose-related gastric ECL cell hyperplasia and ECL cell carcinoids in both male and female rats [see *Clinical Pharmacology* (12.2)].

In rats, lansoprazole also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg per kg per 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 per kg per 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 per kg per day, 2 to 80 times the recommended human 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 mg and 600 mg

lansoprazole per kg per day (40 to 80 times the recommended lansoprazole human dose based on BSA) and female mice treated with 150 mg to 600 mg lansoprazole per kg per 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 per kg per day (10 to 80 times the recommended lansoprazole human dose based on BSA).

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

Lansoprazole was negative in the Ames test, the *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) test, the *in vivo* mouse micronucleus test and the rat bone marrow cell chromosomal aberration test. Lansoprazole was positive in *in vitro* human lymphocyte chromosomal aberration tests.

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

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

## 14 CLINICAL STUDIES

### 14.1 Healing of Erosive Esophagitis

Two multi-center, double-blind, active-controlled, randomized, 8-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: KAPIDEX 60 mg daily, KAPIDEX 90 mg daily or lansoprazole 30 mg 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 5.

Table 5: EE Healing Rates<sup>a</sup>: All Grades

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

CI = Confidence interval

<sup>a</sup> Based on crude rate estimates, patients who did not have endoscopically documented healed EE and prematurely discontinued were considered not healed.

<sup>b</sup> Patients with at least one post baseline endoscopy

<sup>c</sup> Primary efficacy endpoint

<sup>d</sup> Demonstrated non-inferiority to lansoprazole

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

### 14.2 Maintenance of Healed Erosive Esophagitis

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 were evaluated with KAPIDEX 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.

Sixty-six percent of patients treated with 30 mg of KAPIDEX remained healed over the six-month time period as confirmed by endoscopy (see Table 6).

**Table 6: Maintenance Rates<sup>a</sup> of Healed EE at Month 6**

| Number of Patients (N) <sup>b</sup> | Treatment Group (daily) | Maintenance Rate (%) |
|-------------------------------------|-------------------------|----------------------|
| 125                                 | KAPIDEX 30 mg           | 66.4 <sup>c</sup>    |
| 119                                 | Placebo                 | 14.3                 |

<sup>a</sup> Based on crude rate estimates, patients who did not have endoscopically documented relapse and prematurely discontinued were considered to have relapsed.

<sup>b</sup> Patients with at least one post baseline endoscopy

<sup>c</sup> Statistically significant vs placebo

KAPIDEX 60 mg was studied and did not provide additional clinical benefit over KAPIDEX 30 mg.

KAPIDEX 30 mg demonstrated a higher median percent of 24-hour heartburn-free days compared to placebo over the 6-month treatment period.

### 14.3 Symptomatic Non-Erosive GERD

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

KAPIDEX 30 mg provided statistically significantly greater percent of days with heartburn-free 24-hour periods over placebo as assessed by daily diary over 4 weeks (see Table 7). KAPIDEX 60 mg was studied and provided no additional clinical benefit over KAPIDEX 30 mg.

**Table 7: Median Percentages of 24-Hour Heartburn-Free Periods During the 4 Week Treatment Period of the Symptomatic Non-Erosive GERD Study**

| N   | Treatment Group (daily) | Heartburn-Free 24-hour Periods (%) |
|-----|-------------------------|------------------------------------|
| 312 | KAPIDEX 30 mg           | 54.9 <sup>a</sup>                  |
| 310 | Placebo                 | 18.5                               |

<sup>a</sup> Statistically significant vs placebo

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

## 16 HOW SUPPLIED/STORAGE AND HANDLING

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

| <b>NDC Number</b> | <b>Size</b>              |
|-------------------|--------------------------|
| 64764-905-11      | Unit dose package of 100 |
| 64764-905-30      | Bottle of 30             |
| 64764-905-90      | Bottle of 90             |
| 64764-905-19      | Bottle of 1000           |

KAPIDEX delayed release capsules, 60 mg, are opaque, blue with TAP and "60" imprinted on the capsule and supplied as:

| <b>NDC Number</b> | <b>Size</b>              |
|-------------------|--------------------------|
| 64764-915-11      | Unit dose package of 100 |
| 64764-915-30      | Bottle of 30             |
| 64764-915-90      | Bottle of 90             |
| 64764-915-19      | Bottle of 1000           |

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature]

## 17 PATIENT COUNSELING INFORMATION

[see FDA-Approved Patient Labeling (17.2)]

### 17.1 Information for Patients

To ensure the safe and effective use of KAPIDEX, this information and instructions provided in the FDA-approved patient labeling should be discussed with the patient. Inform patients of the following:

KAPIDEX is available as a delayed release capsule.

KAPIDEX may be taken without regard to food.

KAPIDEX should be swallowed whole.

- Alternatively, KAPIDEX capsules can be opened and administered as follows:
  - Open capsule;
  - Sprinkle intact granules on one tablespoon of applesauce;
  - Swallow immediately.

### 17.2 FDA-Approved Patient Labeling

Patient Labeling for  
KAPIDEX (cap-i-decks)  
(dexlansoprazole)  
delayed release capsules

Please read this information carefully before you start taking KAPIDEX. Also, read this information each time you refill your prescription, in case anything has changed. Remember, this information does not take the place of talking with your doctor.

#### What is KAPIDEX?

KAPIDEX is a medicine called a proton pump inhibitor (PPI). Take it for as long as your doctor tells you. KAPIDEX reduces the amount of acid in your stomach.

KAPIDEX is used in adults:

- To treat heartburn related to gastroesophageal reflux disease (GERD).
- To heal acid-related damage to the lining of the esophagus (called erosive esophagitis or EE).
- To stop erosive esophagitis from coming back.

#### What is GERD and EE?

GERD happens when acid from your stomach enters the tube (esophagus) that connects your mouth to your stomach. This may cause a burning feeling in your chest or throat, sour taste or burping.

In some cases, acid can damage the lining of your esophagus. This damage is called erosive esophagitis or EE.

#### Who Should Not Take KAPIDEX?

The active ingredient in KAPIDEX is dexlansoprazole. You should not take KAPIDEX if you are allergic to KAPIDEX or any of its ingredients [see What is in KAPIDEX?].

#### What Should I Tell My Doctor Before and While I Take KAPIDEX?

Tell your doctor about all your medical conditions. Be sure to tell your doctor if you:

- Are pregnant or could be pregnant
- Are breastfeeding
- Have liver problems

Tell your doctor about all your medicines, including any prescription and any non-prescription medicines, herbal remedies, and vitamins.

KAPIDEX and certain other medicines can affect each other. Before taking KAPIDEX, tell your doctor if you are taking:

- ampicillin
- atazanavir
- digoxin
- iron
- ketoconazole
- warfarin

#### How Should I Take KAPIDEX?

Take this medicine exactly as it was prescribed and for the full length of time.

You can take KAPIDEX with or without food.

KAPIDEX should be swallowed whole.

KAPIDEX capsules can also be opened and the contents sprinkled on a tablespoon of applesauce. Swallow immediately.

If you miss a dose of KAPIDEX, take your KAPIDEX as soon as you remember. If you think you took too much medicine, call your doctor.

**What Are the Possible Side Effects of KAPIDEX?**

The most common side effects of KAPIDEX were diarrhea, stomach pain, nausea, common cold, vomiting and gas. There are other less common side effects. If you have any symptoms, be sure to tell your doctor about them.

Call your doctor right away if you have any of the above side effects or any other side effects that worry you while using KAPIDEX. Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

**What Else Should I Know When Taking KAPIDEX?**

KAPIDEX may stop your pain and other acid related symptoms, but you could still have serious stomach problems.

**General Information**

Medicines are sometimes prescribed for conditions other than those listed in the patient labeling. Do not give KAPIDEX to other people, even if they have the same symptoms you have. Ask your doctor about any concerns you may have or if you want more information about KAPIDEX.

Keep KAPIDEX and all other medicines out of the reach of children. Store KAPIDEX at room temperature.

For full product information, call 1-866-985-2743.

**What is in KAPIDEX?**

*Active ingredient:* dexlansoprazole.

*Inactive ingredients:* sugar spheres, magnesium carbonate, sucrose, low-substituted hydroxypropyl cellulose, titanium dioxide, hydroxypropyl cellulose, hypromellose 2910, talc, methacrylic acid copolymer, polyethylene glycol 8000, triethyl citrate, polysorbate 80, and colloidal silicon dioxide. The capsule shell is made of hypromellose, carrageenan and potassium chloride. Based on the capsule shell color, blue contains FD&C Blue No.2 and aluminum lake; gray contains ferric oxide and aluminum lake; and both contain titanium dioxide.

Distributed by

**Takeda Pharmaceuticals America, Inc.**

Deerfield, IL 60015

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