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K-CAB Box Insert

DIMENSION: 160 mm x 370 mm
FONT SIZE: Title header copies: 6.4 pt, Detail copies: 6.4 pt

160 mm

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Tegoprazan

K-CAB®

Film-Coated Tablets 50mg
Potassium-Competitve Acid Blocker

PRODUCT DESCRIPTION

A light pink, asymmetric triangle, film-coated tablet, marked with "CJ" on one side and "50" on the other side.

FORMULATION

Each film-coated tablet contains:
Tegoprazan 50.0mg

List of excipients:
D-mannitol, microcrystalline cellulose, croscarmellose sodium, hydroxypropylcellulose, colloidal silicon dioxide, magnesium stearate, opadry II pink (85 F240134): PVA (polyvinyl alcohol), titanium dioxide, PEG (polyethylene glycol), talc, iron oxide red.

PHARMACODYNAMICS

Mechanism of Action:

Tegoprazan is a potassium-competitive acid blocker (P-CAB) that reversibly blocks gastric acid secretion by competitively binding with potassium to the proton pumps (H+/K+-ATPase) present in gastric wall cells. Tegoprazan binds in a concentration-dependent manner and blocks gastric acid secretion. Binding has reversibility. Tegoprazan inhibits the proton pump directly without activation by acid.

Pharmacodynamic Effects:

After single and multiple oral dosing with 50 mg and 100 mg of tegoprazan to healthy subjects, tegoprazan showed rapid and potent inhibitory effects on gastric acid secretion from the first dose. Intragastric pH above 4 was reached within 1 hour. The 24-hr pH 4 holding time ratio after single dosing with 50mg and 100mg of tegoprazan were 55.07% to 68.38%, respectively. After 7 days of multiple dosing with 50 mg and 100 mg of tegoprazan, the 24-hr pH 4 holding time ratio were 58.35% and 66.55%, respectively. Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown. After multiple oral dosing with 100 mg tegoprazan, the gastrin level was significantly increased compared to the baseline during treatment period. However, it was returned to baseline level in safety follow up visit after the treatment period was over. It has been reported that there is a potential risk of change in normal intestinal flora and proliferation of harmful bacteria such as *Salmonella, Campylobacter, Clostridium difficile* due to decrease in gastric acidity when taking acid suppressants. Treatment with tegoprazan also may lead to increased risk of gastrointestinal infections.

Clinical Efficacy and Safety:

- Erosive Gastroesophageal Reflux Disease:

A randomized, double-blind, active-controlled, comparative phase III study was conducted in 302 patients with erosive gastroesophageal reflux disease to evaluate K-CAB 50mg, 100mg or esomeprazole 40mg for up to 8 weeks. The cumulative healing rate at week 8 was 98.91%(91 patients/92 patients), 98.90%(90 patients/91 patients), and 98.86%(87 patients/88 patients), respectively, in the K-CAB 50mg, 100mg and 40mg esomeprazole treatment groups, demonstrating non-inferiority.

- Non - Erosive Gastroesophageal Reflux Disease

A randomized, double-blind, placebo-controlled, phase III study was conducted in 324 patients with non-erosive gastroesophageal reflux disease to evaluate K-CAB 50 mg, 100 mg or placebo for 4 weeks. The rate of patients with complete resolution of main symptoms, heartburn and reflux of gastric acid, at week 4 was 42.45% (45 patients/106 patients), 48.48% (48 patients/99 patients), 24.24% (24 patients/99 patients), respectively in treatment group of K-CAB 50mg, 100mg and placebo, demonstrating superiority.

- Gastric Ulcer

A randomized, double-blind, active-controlled, comparative phase III study was conducted in 306 patients with gastric ulcer to evaluate K-CAB 50mg, 100mg or lansoprazole 30mg for up to 8 weeks. The cumulative healing rate at week 8 was 100.00%(88 patients/88patients), 97.85%(91 patients/93 patients), and 100.00%(85 patients/85 patients), respectively, in the K-CAB 50mg, 100mg and 30mg lansoprazole treatment groups, demonstrating non-inferiority.

- Eradication of *H. pylori* concurrently given with appropriate antibiotic therapy treatment in patients with peptic ulcer and/or chronic atrophic gastritis:

A randomized, double-blind, active-controlled, comparative phase III study was conducted in 350 patients with peptic ulcer and/or chronic atrophic gastritis who are positive for H. pylori to evaluate K-CAB 50 mg or lansoprazole 30 mg in combination with amoxicillin 1 g and clarithromycin 500 mg twice daily for 7 days. The H. pylori eradication rate was 69.33% (104 patients/150 patients) and 67.33% (101 patients/150 patients), respectively, in the K-CAB 50 mg and 30 mg lansoprazole with antibiotic combination therapy treatment groups, demonstrating non-inferiority.

PHARMACOKINETICS

- Absorption

Tmax of tegoprazan following single oral dose to healthy adults was ranged from 0.5 to 1.5 hours across the doses tested 50-400mg. After single administration, the mean peak plasma concentration (Cmax) and the mean exposure level (AUC) tended to increase dose proportionally within the administration dose range. After 7 days of repeated administration, the mean peak plasma concentration of each dose group was similar or decreased in comparison with that of single administration. Food effects on bioavailability were evaluated after administration of 200 mg of oral tegoprazan fasting and after meals to healthy adults. Although there was a tendency to delay the Tmax and decrease the Cmax after food intake, there was no significant difference on the AUClast and pharmacodynamic parameter (the maintenance time of intragastric acidity above pH 4).

- Distribution:

The proportion of in vitro non-protein-binding drug was 8.7 ~ 9.0% human in the concentration range of 1~10μM.

- Metabolism and Excretion

Tegoprazan is mainly metabolized by CYP3A4. The main metabolite is a metabolite M1 (dealkylated metabolite). After intravenous administration of tegoprazan to rats and dogs, the amount of unchanged tegoprazan excreted in urine was less than 1%. After oral administration of [14C]-tegoprazan to rats, recovery of radioactivity at 168 hours (of dosing) were 93% and 97% in the female and male, respectively. 22% to 24% of the total radioactivity was excreted in urine, and 65% to 69% was eliminated in feces in both female and male rats. After oral administration to rats with biliary intubation, tegoprazan was excreted 41.4% in bile acid, 25.7% in urine and 28.4% in feces. And the total recovery of radioactivity was 97.7%. Less than 1% of unchanged tegoprazan was found 1% in bile acid and urine, 15% was in feces. 6% of metabolite M1 was found in feces. Following the administration of tegoprazan to healthy male subjects, the plasma elimination half-life of unchanged tegoprazan and metabolite M1 were 4.1 hours and 22.8 hours, respectively. Urinary excretion rate of the unchanged tegoprazan was approximately 4.1% and the clearance was 1.1L/hr. Urinary excretion rate of the major metabolite M1 was about 2.3% and the clearance was 0.5L/hr.

INDICATIONS

K-CAB is indicated for the treatment of Erosive Gastroesophageal Reflux Diseases, Non-Erosive Gastroesophageal Reflux Disease and Gastric Ulcer. K-CAB is also indicated for the eradication of *H. pylori* when concurrently given with appropriate antibiotic therapy treatment in patients with peptic ulcer and/or chronic atrophic gastritis

DOSAGE AND MODE OF ADMINISTRATION

For Adult Population:

- Treatment of Erosive Gastroesophageal Reflux Disease:

50 mg once daily for 4 weeks. For patients who do not heal or have persistent symptoms after 4 weeks, an additional 4-week treatment may be considered.

- Treatment of Non-Erosive Gastroesophageal Reflux Disease:

50 mg once daily for 4 weeks.

- Treatment of Gastric Ulcer:

50 mg once daily for 8 weeks.

- Eradication of *H. pylori* concurrently given with appropriate antibiotic therapy treatment in patients with peptic ulcer and/or chronic atrophic gastritis:

Patients with *H. pylori* infection should be treated with eradication therapy. Tegoprazan 50 mg, clarithromycin 500 mg, and amoxicillin 1 g are orally administered twice daily for 7 days.
When selecting appropriate combination therapy, consideration should be given to official national, regional and local guidance regarding bacterial resistance, duration of treatment and appropriate use of antibacterial agents.

K-CAB can be taken orally without regard to food.

For Pediatric Population:

Clinical safety and efficacy of K-CAB in Pediatric and adolescent patients have not been established.

CONTRAINDICATIONS

Patients with hypersensitivity to the tegoprazan, any of the product components or substituted benzimidazoles. Patients who take atazanavir, nelfinavir or rilpivirine-containing products. Pregnant women or nursing mothers.

WARNINGS AND PRECAUTIONS

- In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with K-CAB may alleviate symptoms and delay diagnosis.
- Cyanocobalamin (Vitamin B12) deficiency: Daily treatment with any acid-suppressing medications over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.
- Bone Fracture: Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose (defined as multiple daily doses) and long-term PPI therapy (a year or longer). Patients should use the appropriate dose and shortest duration of K-CAB therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines.
- Hypomagnesemia has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPIs. For patients expected to be on prolonged treatment or who take K-CAB 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 treatment and periodically. Serious adverse events include tetany, arrhythmias, and seizures.
- Decreased gastric acidity due to proton pump inhibitors, increases counts of bacteria normally present in the gastrointestinal tract. Treatment with gastric acid suppressants may possibly increase the risk of gastrointestinal infections such as *Salmonella, Campylobacter and Clostridium difficile*. Published observational studies suggest that PPI therapy may be associated with an increased risk of *Clostridium difficile*-associated diarrhea (CDAD), especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. CDAD has been reported with use of nearly all antibacterial agents, Patients should use the lowest dose and shortest duration of K-CAB therapy appropriate to the condition being treated.

CDAD has been reported with use of nearly all antibacterial agents. For more information, specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with tegoprazan, refer to Warnings and Precautions sections of those package inserts.

- Hepatic Impairment: There is no data on patients with hepatic impairment.
- Renal Impairment: There is no data on patients with renal impairment.
- Elderly People: In general, it should be administered to the elderly patients with caution, keeping in mind the greater frequency of decreased physiological functions, such as liver or kidney.

PREGNANCY AND LACTATION

- Pregnant Women:

There is no safety data for exposure to tegoprazan in pregnant women. In an embryo-fetal development study, short supernumerary cervical ribs were observed with higher incidence in rats, Therefore K-CAB is contraindicated during pregnancy.

- Nursing Mothers:

As it is not known whether tegoprazan is excreted into human milk, discontinue nursing while taking K-CAB. Excretion of tegoprazan into milk has been reported in rats.

INTERACTIONS

- Drugs Dependent on Gastric pH for Absorption:

Due to its effects on gastric acid secretion, tegoprazan can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Like with other drugs that decrease the intragastric acidity, the absorption of drugs such as ketoconazole, itraconazole, ampicillin ester, atazanavir, iron salts, erlotinib, gefitinib and mycophenolate mofetil (MMF) can decrease during treatment with tegoprazan. While absorption of drugs such as digoxin can increase during treatment with K-CAB. Because tegoprazan inhibits gastric acid secretion, co-administration of atazanavir, nelfinavir and rilpivirine with tegoprazan is expected to decrease plasma concentration of atazanavir, nelfinavir or rilpivirine which is dependent on gastric pH for absorption, results in a loss of the therapeutic effect. Therefore, concomitant use of atazanavir, nelfinavir and rilpivirine with K-CAB is contraindicated.

- Tegoprazan is mainly metabolized by CYP3A4. Concomitant use of clarithromycin, a CYP3A4 inhibitor, with tegoprazan has increased AUC_τ of tegoprazan and clarithromycin by 2.5 times and 1.25 times, respectively.
- Tegoprazan has been shown to have no significant effects on the pharmacokinetics of amoxicillin.

ADVERSE DRUG REACTION

1) A total of 5 clinical studies were conducted with erosive gastroesophageal reflux disease and non-erosive gastroesophageal reflux disease and gastric ulcer patients. 360 patients were treated with tegoprazan 50 mg. Adverse events and adverse drug reactions (marked with *) reported during the clinical trials are as following;

Common adverse events reported (≥1%) in tegoprazan 50 mg treatment group are presented in Table 1.

Table 1. Adverse events reported in ≥1% patients from clinical trials

Body System	Adverse Events
Gastrointestinal	Nausea, diarrhea, dyspepsia
Infections and Infestations	Nasopharyngitis, viral upper respiratory tract Infection
General Disorders and Administration Site Conditions	Chest discomfort

Less common adverse events reported in <1% patients after administration of K-CAB 50 mg from clinical studies are listed below by body system;

- *Gastrointestinal Disorders:* abdominal pain upper*, abdominal discomfort*, constipation*, abdominal pain*, abdominal distension*, vomiting, eructation, abdominal pain lower, gastric ulcer*, anal haemorrhage, erosive duodenitis*, flatulence*, gastric polyps*, gastroesophageal reflux disease*, intestinal metaplasia, haematemesis, hemorrhoids, melaena*
- *Infections and Infestations:* folliculitis*, gastroenteritis bacterial, latent tuberculosis
- *Laboratory Investigations:* alanine aminotransferase increased*, aspartate aminotransferase increased*, gamma-glutamyltransferase increased*, blood bilirubin increased, blood creatine phosphokinase increased*, blood urine present, red blood cells urine positive, blood gastrin increased*, blood triglycerides increased*
- *General Disorders and Administration Site Conditions:* fatigue*
- *Injury, Poisoning and Procedural Complications:* ligament sprain, concussion, excoriation, foot fracture, joint injury, muscle strain
- *Musculoskeletal and Connective Tissue Disorders:* myalgia*, arthralgia*, tendonitis*
- *Nervous System Disorders:* headache*, dizziness
- *Skin and Subcutaneous Tissue Disorders:* angioedema, dermatitis, seborrheic dermatitis*
- *Respiratory, Thoracic and Mediastinal Disorders:* cough*, oropharyngeal pain, throat irritation
- *Reproductive System and Breast Disorders:* vaginal discharge, vulvovaginal pruritus, breast calcifications*, adenomyosis, ovarian cyst
- *Hepatobiliary Disorders:* bile duct stone, hepatic cyst
- *Renal and Urinary Disorders:* hypertonic bladder*, nocturia, renal cyst
- *Neoplasms Benign, Malignant and Unspecified:* breast cancer, gastrointestinal tract adenoma*, adenocarcinoma gastric, uterine leiomyoma
- *Cardiac Disorders:* ventricular extrasystoles*
- *Blood and Lymphatic System Disorders:* lymphadenitis*, anaemia*
- *Psychiatric Disorders:* insomnia*
- *Surgical and Medical Procedures:* dental implantation
- *Ear and Labyrinth Disorders:* ear pain*
- *Metabolism and nutrition disorders:* diabetes mellitus
- *Vascular disorder:* hypertension
- *Endocrine disorders:* thyroid cyst*

2) A clinical study was conducted in patients with peptic ulcer and/or chronic atrophic gastritis who were positive for *H.pylori.* 172 patients were treated with tegoprazan 50 mg, in combination with amoxicillin 1 g and clarithromycin 500 mg. Adverse events and adverse drug reactions (marked with *) reported during the clinical trial is as following;

Common adverse events reported (≥1%) in tegoprazan 50 mg in combination with amoxicillin 1g and clarithromycin 500 mg treatment group are presented in Table 2.

Table 2. Adverse events reported in ≥1% patients from clinical trials

Body System	Adverse Events
Gastrointestinal	Nausea*, diarrhea*, dyspepsia*, abdominal pain upper*, abdominal pain*, abdominal distention*
Laboratory Investigations	CPK increased*
Infections and Infestations	Cystitis*
General Disorders and Administration Site Conditions	Asthenia*
Nervous System Disorders	Headache*, dizziness*, dysgeusia*
Skin and Subcutaneous Tissue Disorders	Urticaria*, pruritus*, erythema*

Less common adverse events reported in <1% patients after administration of K-CAB 50 mg in combination with amoxicillin 1g and clarithromycin 500 mg from clinical studies are listed below by body system;

- Gastrointestinal Disorders: vomiting, anal incontinence*
- Infections and Infestations: folliculitis*, tonsillitis*
- Skin and Subcutaneous Tissue Disorders: rash*, drug eruption*, toxic skin eruption*
- Cardiac Disorders: palpitation*
- Laboratory Investigations: AST increased, LDH increased*
- Nervous System Disorders: migraine*
- Respiratory, Thoracic and Mediastinal Disorders: oropharyngeal pain, dysphonia
- Vascular Disorders: hot flush*, flushing*

OVERDOSE

There have been no reports of significant overdose with tegoprazan. In clinical trials, there have been cases where up to 400mg of this drug has been administered to healthy adults. In the event of an overdose with K-CAB, the patients should be monitored for poisoning symptoms and treatment should be supportive if necessary.

STORAGE CONDITION

Store at or below 30°C in the original package. Keep out of sight and reach of children.

PRESENTATION

50 mg film-coated tablets: Alu/Alu PTP blister pack (30 tablets/box), PP plug/HDPE bottle (30 and 300 tablets per bottle).
Not all presentations may be available locally.

PRODUCT REGISTRANT
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FRONT VIEW

BACK VIEW