Tegoprazan

K-CAB®

25 mg Film-Coated Tablet

50 mg Film-Coated Tablet

Potassium - Competitive Acid Blocker

Name of Medicinal Product
K-CAB 50mg Film-Coated Tablet
K-CAB 25mg Film-Coated Tablet

Each 1 film-coated tablet contains
Tegoprazan.....50.0 mg
Tegoprazan.....25.0 mg

Excipients: D-Mannitol, Microcrystalline Cellulose, Croscarmellose Sodium, Hydroxypropylcellulose, Colloidal Silicon Dioxide, Magnesium Stearate and Opadry II Pink

Product Description
A light pink, oblong, film-coated tablet, engraved with “K|50” on one side and “|” on the other.
A light pink, oblong, film-coated tablet, engraved with “K|25” on one side and “|” on the other.

Indication
1. Treatment of Erosive Gastroesophageal Reflux Disease
2. Treatment of Non-Erosive Gastroesophageal Reflux Disease
3. Treatment of Gastric Ulcer
4. Eradication of *H. pylori* concurrently given with appropriate antibiotic therapy treatment in patients with peptic ulcer and/or chronic atrophic gastritis
5. Maintenance of healed Erosive Gastroesophageal Reflux Disease. <25 mg only>

Dosage and Administration
Adults:
1. 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.
2. Treatment of Non-Erosive Gastroesophageal Reflux Disease
- 50 mg once daily for 4 weeks.
3. Treatment of Gastric Ulcer
- 50 mg once daily for 8 weeks.
4. 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. K-CAB 50 mg, clarithromycin 500 mg, and amoxicillin 1 g are orally administered twice daily for 7 days.
5. Maintenance of healed Erosive Gastroesophageal Reflux Disease. <25 mg only>
- 25 mg once daily for up to 24 weeks.

K-CAB can be taken without regard to food.

Route of Administration
Oral route

Contraindications
1) (Patients with) hypersensitivity to tegoprazan, any of the excipients or substituted benzimidazoles
2) Patients who take atazanavir, nelfinavir or rilpivirine-containing products (see Interaction with Other Medicaments)
3) Pregnant women or nursing mothers (see Pregnancy and Lactation)

Warnings and Precaution
General Precaution
1) 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 tegoprazan may alleviate symptoms and delay diagnosis.

2) 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 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.

3) Patient should be monitored regularly when treated with tegoprazan for long term.

4) Gastric polyp was observed with long term use of P-CABs and tegoprazan.

5) Maintenance of Erosive Gastroesophageal Reflux Disease: Do not administer to patients who do not require maintenance therapy.

6) Gastric ulcer: Clinical experience on long term use is insufficient. Do not administer for patient who do not require maintenance therapy.

7) 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 tegoprazan therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines.

8) 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 tegoprazan 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 reactions include tetany, arrhythmias, and seizures.

9) Decreased gastric acidity due to PPIs, 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 tegoprazan therapy appropriate to the condition being treated.

10) Fundic gland polyps: Risk of fundic gland polyps increases with long-term use of PPIs, especially beyond one year. Fundic gland polyps are mostly asymptomatic. Use the shortest duration and the lowest dose of PPI and tegoprazan according to symptoms.

Use in Specific Populations

1) Paediatric use

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

2) Elderly People

In general, K-CAB should be administered to the elderly patients with caution, keeping in mind the greater frequency of decreased physiological functions, such as liver or kidney.

3) Renal Impairment

Safety and efficacy of K-CAB have not been established in patients with renal impairment.

4) Hepatic Impairment

Safety and efficacy of K-CAB have not been established in patients with hepatic impairment.

Effect on Ability to Drive and Use Machine

No studies on the effects on the ability to drive and use machines have been performed for tegoprazan, and the loss of this ability cannot be predicted from its pharmacological action. Nevertheless, when considering the patient's ability to drive and use machines, the clinical condition of the patient and the adverse reactions of the drug should be considered.

Interaction with Other Medicaments

1) 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 tegoprazan.
Because tegoprazan inhibits gastric acid secretion, co-administration of atazanavir, nelfinavir and rilpivirin with tegoprazan is expected to decrease plasma concentration of atazanavir, nelfinavir or rilpivirin 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 tegoprazan is contraindicated.

2) Tegoprazan is mainly metabolized by CYP3A4. Concomitant use of clarithromycin, a CYP3A4 inhibitor, with tegoprazan has increased AUC_T of tegoprazan and clarithromycin by 2.5 times and 1.25 times, respectively.

3) Tegoprazan has been shown to have no effects on the pharmacokinetic profiles of amoxicillin.

4) Tegoprazan has been shown to have no effects on the pharmacokinetic profiles of atorvastatin.

5) Concomitant use of tegoprazan and NSAIDs (Naproxen, Aceclofenac or Celecoxib) has been shown to have no clinically significant effects on the pharmacokinetic profiles.

6) Effects of other drugs on tegoprazan

① Tegoprazan is metabolized in liver by CYP3A4. In vitro studies have shown that ketoconazole, a CYP3A4 inhibitor, significantly inhibited the metabolism of tegoprazan, and while inhibitors of CYP1A2, CYP2C9, CYP2C19, CYP2D6 did not significantly reduced the metabolism of tegoprazan. Concomitant use of tegoprazan with CYP3A4 inhibitors may elevate exposure of tegoprazan.

② Tegoprazan is a substrate of P-gp. *In vitro* studies have shown that the efflux ratio of tegoprazan was decreased by verapamil, a P-gp inhibitor. Co-administration of tegoprazan and P-gp inhibitors may result in increase of exposure by increasing gastrointestinal absorption of tegoprazan.

③ In healthy adult subjects, co-administration of tegoprazan with clarithromycin (substrates and inhibitors of CYP3A4 and P-gp) resulted in increase of $C_{ss,max}$ and AUC_T of tegoprazan by 1.65 times and 2.5 times, respectively. AUC_T of clarithromycin increased slightly by 1.25 times and there was no significant increase of $C_{ss,max}$. Neither adverse reactions nor adverse drug reaction clinically significant were observed.

④ In healthy adult subjects, co-administration of tegoprazan with metronidazole, tetracycline and bismuth resulted in decrease of the AUC_{0-12} and $C_{ss,max}$ of tegoprazan by 0.78 times and by 0.75 times, respectively, and the AUC_{0-12} of tegoprazan metabolite M1 decreased by 0.77 times and $C_{ss,max}$ by 0.84 times, compared to when tegoprazan was administered alone. However, no clinically significant adverse reactions or adverse drug reactions were observed.

7) Effects of tegoprazan on other drugs

① *In vitro* studies have shown that tegoprazan showed competitive inhibition against CYP2C8 and CYP3A4. But, the IC_{50} values were approximately 25-fold greater than the peak plasma concentration of the recommended human dose.

② For OATP1B1, there was a difference in the inhibitory activity of tegoprazan depending on substrates and it is expected that the plasma concentrations of some drugs which are substrate for OATP1B1 may be increased slightly considering the C_{max} at the clinical doses.

③ As a result of co-administration of tegoprazan with metronidazole, tetracycline and bismuth to healthy adults, compared to the co-administration of metronidazole, tetracycline and bismuth, the pharmacokinetics of metronidazole was not affected, and the AUC_{0-6} of tetracycline was decreased by 0.62 times, $C_{ss,max}$ decreased by 0.64 times, AUC_{0-6} of bismuth increased by 1.55 times, and $C_{ss,max}$ increased by 1.38 times, but no clinically significant adverse reactions or adverse drug reactions were observed.

Incompatibilities
Not applicable.

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 a 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.

Adverse Reactions
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

reactions and adverse drug reactions (marked with *) reported during the clinical trials are as following;

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

Table 1. Adverse reactions (%) reported in ≥ 1% patients from clinical trials

System Organ Class	Adverse reactions
Gastrointestinal Disorders	Nausea*, Diarrhoea*, Dyspepsia*
Infections and Infestations	Nasopharyngitis*, Viral upper respiratory tract infection*
General disorders and administration site conditions	Chest discomfort*

Less common adverse reactions reported in <1% patients after administration of tegoprazan 50 mg from clinical studies are presented in Table 2.

Table 2. Adverse events (%) reported in <1% patients from clinical trials

System Organ Class	Adverse reactions
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
Investigations	Alanine aminotransferase increased*, Gamma glutamyltransferase increased*, Blood bilirubin increased, Aspartate aminotransferase 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, Seborrhoeic 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 (including cysts and polyps)	Adenocarcinoma gastric, Breast cancer, Gastrointestinal tract adenoma*, 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*

Two clinical studies were conducted in patients with peptic ulcer and/or chronic atrophic gastritis who were positive for *H.pylori.* 314 patients were treated with tegoprazan 50 mg, in combination with amoxicillin 1 g and clarithromycin 500 mg. Adverse reactions and adverse drug reactions (marked with *) reported during the clinical trial is as following;

Common adverse reactions events reported (≥ 1%) in tegoprazan 50 mg in combination with amoxicillin 1 g and clarithromycin 500 mg treatment group are presented in Table 3.

Table 3. Adverse reactions (%) reported in ≥ 1% patients from clinical trials

System Organ Class	Adverse reactions
Gastrointestinal Disorders	Diarrhea*, Abdominal pain upper*, Abdominal distension*, Dyspepsia*, Nausea*, Abdominal pain*
Nervous System Disorders	Dysgeusia*, Headache*
Skin and Subcutaneous Tissue Disorders	Urticaria*

Less common adverse reactions reported in <1% patients after administration of tegoprazan 50 mg in combination with amoxicillin 1 g and clarithromycin 500 mg from clinical study are presented in Table 4.

Table 4. Adverse reactions (%) reported in <1% patients from clinical trials

System Organ Class	Adverse reactions
Gastrointestinal Disorders	Constipation*, Dry mouth*, Abdominal discomfort*, Anal incontinence*, Duodenitis, Haematochezia, Paraesthesia oral*, Vomiting
Nervous System Disorders	Dizziness*, Migraine*, Somnolence*, Taste disorder*
Skin and Subcutaneous Tissue Disorders	Pruritus*, Erythema*, Rash*, Drug eruption*, Toxic skin eruption*
Infections and Infestations	Nasopharyngitis, Cystitis, Herpes zoster, Folliculitis*, Hordeolum, Sinusitis, Tonsillitis*
Investigations	Blood creatine phosphokinase increased*, Aspartate aminotransferase increased, Blood triglycerides increased, Blood lactate dehydrogenase increased*
General disorders and administration site conditions	Asthenia*, Chest pain*
Musculoskeletal and Connective tissue disorders	Back pain, Myalgia*, Musculoskeletal stiffness*
Respiratory, Thoracic and Mediastinal Disorders	Dysphonia, Cough, Oropharyngeal pain
Cardiac Disorders	Palpitations*
Vascular Disorders	Hot flush*, Flushing*
Eye Disorders	Choroiditis*, Retinal disorder*
Psychiatric Disorders	Insomnia*
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Colon adenoma
Hepatobiliary Disorders	Hepatic steatosis
Metabolism and nutrition disorders	Type 2 diabetes mellitus

One clinical study was conducted in patients with endoscopically-confirmed healed erosive gastroesophaeal reflux disease. 173 patients were treated with tegoprazan 25mg. Adverse reactions and adverse drug reactions (marked with *) reported during the clinical study is as following:

Table 5. Adverse reactions reported in at least 1% of subjects

System Organ Class	Adverse reactions
Gastrointestinal Disorders	Gastritis erosive*, chronic gastritis*, gastric polyps*, diarrhoea*
Nervous System Disorders	Dizziness*, headache
Infections and Infestations	Nasopharyngitis*
Investigations	Blood creatine phosphokinase increased
Respiratory, Thoracic and Mediastinal Disorders	Cough*

Table 6. Adverse reactions reported in less than 1% of subjects

System Organ Class	Adverse reactions
Gastrointestinal Disorders	Constipation, Hypergastrinaemia*, Abdominal pain*, Intestinal metaplasia, Gastric ulcer, Dyspepsia*, Large intestinal polyp*
Nervous System Disorders	Facial paralysis, Paraesthesia
Infections and Infestations	Cystitis*, Bronchitis*, Gingivitis
Investigations	Alanine aminotransferase increased*, Blood bilirubin increased*, Aspartate aminotransferase increased, Blood triglycerides increased

System Organ Class	Adverse reactions
Musculoskeletal and Connective Tissue Disorders	Scoliosis*, Musculoskeletal discomfort, Intervertebral disc disorder, Osteopenia*, Arthralgia*, Back pain
Injury, Poisoning and Procedural Complications	Contusion, Pelvic fracture, Skin abrasion, Tooth fracture, Wrist fracture
Respiratory, Thoracic and Mediastinal Disorders	Laryngeal ulceration, Productive cough, Oropharyngeal pain
Skin and Subcutaneous Tissue Disorders	Rash, Urticaria chronic, Pruritus
Cardiac Disorders	Diastolic dysfunction
Ear and Labyrinth Disorders	Deafness*
Endocrine Disorders	Thyroid mass*
Hepatobiliary Disorders	Hepatic steatosis*
Renal and Urinary Disorders	Nephrolithiasis

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

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 50 mg and 100 mg of tegoprazan were 55.07% to 68.38%, respectively. After seven 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 studies
1) 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 50 mg, 100 mg or esomeprazole 40 mg 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 50 mg, 100 mg and esomeprazole 40 mg treatment groups, demonstrating non-inferiority. (Table 7)
Table 7. Cumulative healing rate of Erosive Gastroesophageal Reflux Disease at week 8

	K-CAB		Esomeprazole
	50 mg	100 mg	40 mg
PPS	**N=92**	**N=91**	**N=88**
ERD Healing Rate [%(N)]	98.91 (91)	98.90 (90)	98.86 (87)
Difference with	0.05	0.04	

	K-CAB		Esomeprazole
	50 mg	100 mg	40 mg
95% confidence interval	[-3.02, 3.11]	[-3.04, 3.12]	
p-value*	<.0001	<.0001	

* Non-inferiority margin -10%, significance level 0.025(one-sided test), PPS: Per Protocol Set

2) 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. (Table 8)

Table 8. Percentages of patients with complete resolution of main symptoms at week 4 in non-erosive gastroesophageal reflux disease

	K-CAB		Placebo
	50 mg	100 mg	
FAS	**N=106**	**N=99**	**N=99**
Symptom resolution [%(N)]	42.45 (45)	48.48 (48)	24.24 (24)
p-value*	0.0058	0.0004	

* Chi-square test, significance level 0.05(two-sided test), FAS; Full Analysis Set

3) 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/88 patients), 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. (Table 9)

Table 9. Cumulative healing rate of Gastric Ulcer at week 8

	K-CAB		lansoprazole
	50 mg	100 mg	30 mg
PPS	**N=88**	**N=93**	**N=85**
GU Healing Rate [% (N)]	100.00 (88)	97.85 (91)	100.00 (85)
Difference with 95% confidence interval	0.00	-2.15 [-7.66, 2.43]	
p-value*		<0.0001	

* Non-inferiority margin -8.54%, significance level 0.025(one-sided test), PPS: Per Protocol Set

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

Two randomized, double-blind, active-controlled, comparative phase III clinical studies were conducted in *H. pylori* positive patients 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 demonstrated the non-inferiority of K-CAB 50 mg -based triple therapy to lansoprazole 30 mg-based triple therapy. (Table 10)

Table 10. *H. pylori* eradication rate

	Study 1**		Study 2***	
	K-CAB	lansoprazole	K-CAB	lansoprazole
	50 mg with amoxicillin 1 g and clarithromycin 500 mg	30 mg with amoxicillin 1 g and clarithromycin 500 mg	50 mg with amoxicillin 1 g and clarithromycin 500 mg	30 mg with amoxicillin 1 g and clarithromycin 500 mg

PPS	N=150	N=150	N=119	N=112
H. pylori Eradication Rate [% (N)]	69.33(104)	67.33 (101)	71.43 (85)	69.64 (78)
Difference with 95% confidence interval	2.00 [-8.53,12.53]		1.79 [-9.98, 13.55]	
p-value*	0.0127		0.0248	

* Non-inferiority margin -10%, significance level 0.025(one-sided test), PPS: Per Protocol Set
** The study 1 was conducted in patients with peptic ulcer or chronic atrophic gastritis.
*** The study 2 was conducted in patients with peptic ulcer, low-grade mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach, chronic atrophic gastritis, or early gastric cancer patient with malignant tissue completely resected after endoscopic mucosal resection (EMR)/endoscopic submucosal dissection (ESD).

5) Maintenance of healed Erosive Gastroesophageal Reflux Disease

One Phase III, double-blind, randomized, active-controlled study was conducted in patients with endoscopically-confirmed healed erosive gastroesophageal reflux disease, following oral administration of K-CAB 25 mg or lansoprazole 15 mg once daily for 6 months. Primary efficacy endpoint is percentage of subjects maintaining endoscopic remission of upper gastrointestinal tract at week 24, where it is defined as ratio of number of subjects with no endoscopic recurrence of erosion (LA Grade A to D) during maintenance period (24 weeks). The percentage of subjects maintaining endoscopic remission at Week 24 was 90.58% (125 patients/138 patients) in K-CAB 25 mg treatment group and 89.52% (111 patients/124 patients) in lansoprazole 15 mg treatment group. The difference in the endoscopic remission maintenance rate was 1.06% (95% CI, -6.20, 8.33), demonstrating non-inferiority (95% CI, lower bound>-10%)

Table 11. Percentage of subjects maintaining endoscopic remission at week 24

	K-CAB	Lansoprazole
	25 mg	15 mg
PPS	**N=138**	**N=124**
Percentage of subjects maintaining endoscopic remission at week 24 [%(N)]	90.58 (125)	89.52 (111)
Difference with 95% confidence interval	1.06 (-6.20, 8.33)	
p-value*	0.0014	

* Non-inferiority margin -10%, significance level 0.025(one-sided test), PPS: Per Protocol Set

Pharmacokinetics

1) Absorption

T_{max} of tegoprazan following single oral dose to healthy adults was ranged from 0.5 to 1.5 hours across the doses tested 50~400 mg. After single administration, the mean peak plasma concentration (C_{max}) and mean exposure level (AUC) tended to increase dose portionally 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 oral administration of 200 mg of tegoprazan under fasting and after meals to healthy adults. Although there was a tendency to delay the T_{max} and decrease the C_{max} after food intake, there was no significant difference on the AUC_{last} and pharmacodynamic parameter (the maintenance time of intragastric acidity above pH 4).

Food effects on bioavailability were evaluated after administration of 50 mg of oral tegoprazan under fasting, before meals or after meals to healthy adults. Although there was a tendency to delay the T_{max} and decrease the C_{max} after food intake, there was no significant difference on the AUC_{last} and pharmacodynamic parameter (the maintenance time of intragastric acidity above pH 4).

2) Distribution

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

3) Metabolism and Excretion

Tegoprazan is mainly metabolized by CYP3A4. The main metabolite is metabolite M1 (dealkylated metabolite).

After intravenous administration of tegoprazan to rats and dogs, amount of unchanged tegoprazan excreted in urine was less than 1%. After oral administration of [^{14}C]-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.

Nonclinical safety data

1) Mutagenesis

Tegoprazan was negative in the bacterial reverse mutation test using *Salmonella* and *E. coli*. Tegoprazan was positive in the CHL cell chromosome aberration assay, but negative in the in vivo micronucleus test using rat bone marrow cells not to induce micronucleus.

2) Carcinogenesis

In a 2-year carcinogenicity study in rats, gastrointestinal neuroendocrine tumor was observed in the male 15 mg/kg/day (about 4.8 times AUC of the recommended human dose) group and the female 6 mg/kg/day (about 6.8 times AUC of the recommended human dose).

3) Impairment of Fertility

No effects on fertility and early embryonic development were observed up to a high dose of 500 mg/kg/day. As a result of the embryo-fetal development studies, short supernumerary cervical ribs were observed with a higher incidence in rats. The NOAEL for maternal rats was determined to be 500 mg/kg/day, which was 369 times the AUC of the human recommended dose, and the NOEL for embryos and fetuses was determined to be 20 mg/kg/day, which was 15.6 times the AUC of the human recommended dose.

There were no effects on fetal development despite abortions and weight loss symptoms in the maximum dose (10 mg/kg/day) group of rabbit. The NOAEL for maternal rabbits was determined to be 5 mg/kg/day, which was 2 times the AUC of the human recommended dose, and the NOAEL for embryos and fetuses was determined to be 10 mg/kg/day, which was 4.8 times the AUC of the human recommended dose.

In a pre- and post-natal development study and maternal function study in rats, tegoprazan and metabolite M1 were shown to be excreted in breast milk. And the NOAEL was determined to be 20 mg/kg/day, which was 8 times the AUC of the human recommended dose on the basis of the decreased survival rate of the first filial rats at 60 mg/kg/day, the maximal dose.

Instructions for Use and Handling

See Dosage and Administration

Storage Condition

Store below 30℃

Shelf Life

36 months

Dosage Forms and Packaging Available

10 tablets per plain aluminium foil / aluminium film blister.
Each pack contains 30 film-coated tablets.

Name and Address of Manufacturer

239, Osongsaengmyeong 2-ro,
Osong-eup, Heungdeok-gu, Cheongju-si,
Chungcheongbuk-do, Republic of Korea

Product Registration Holder
Pharmaniaga Marketing Sdn. Bhd. (198401005734),
No. 7, Lorong Keluli 1B,
Kawasan Perindustrian Bukit Raja Selatan, Seksyen 7, 40000 Shah Alam, Selangor Darul Ehsan, Malaysia

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