SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

K-CAB Tablet 50 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablets contains: Tegoprazan 50 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

In adult

- 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.

  K-CAB Tablet 50 mg can be taken without regard to food.

  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.

Pediatric population

Clinical safety and efficacy of K-CAB Tablet 50 mg in pediatric and adolescent patients have not been established.

4.3 Contraindications

- (Patients with) Hypersensitivity to the tegoprazan, any of the product components listed in section 6.1. or substituted benzimidazoles
- Patients who take atazanavir or rilpivirine-containing products
- Pregnant women or nursing mothers

4.4 Special warnings and precautions for use

General 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 Tablet 50 mg 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 Tablet 50 mg 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 PPI (Proton Pump Inhibitor)s. For patients

expected to be on prolonged treatment or who take K-CAB Tablet 50 mg 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 Tablet 50 mg therapy appropriate to the condition being treated.

* The following patients should be treated with caution

- 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.
- Pediatric population: Clinical safety and efficacy of K-CAB Tablet 50 mg in pediatric and adolescent patients have not been established.

4.5 Interaction with other medicinal products and other forms of interaction

- 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 Tablet 50 mg. 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 K-CAB Tablet 50 mg is contraindicated.

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

4.6 Pregnancy and lactation

- Pregnancy

  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 Tablet 50 mg is contraindicated during pregnancy.

- Lactation

  As it is not known whether tegoprazan is excreted into human milk, discontinue nursing while taking K-CAB Tablet 50 mg. Excretion of tegoprazan into milk has been reported in rats.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed for K- CAB Tablet 50 mg, 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.

4.8 Undesirable effects

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;

Adverse events reported in at least 1% of subjects

Body system	Adverse events
Gastrointestinal	Nausea, Diarrhea, Dyspepsia, Abdominal pain upper
Infections and Infestations	Nasopharyngitis, Viral upper respiratory tract infection
General disorders and administration site conditions	Chest discomfort

Adverse events reported in less than 1% of subjects

Body system	Adverse events
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, Hematemesis, 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 disorders and mediastinal	Cough*, Oropharyngeal pain, Throat irritation, Nasopharyngitis*
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;

Adverse events reported in at least 1% of subjects

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*

Adverse events reported in less than 1% of subjects

Body System	Adverse Events
Gastrointestinal	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*

4.9 Overdose

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 overdose with K-CAB Tablet 50 mg, the patients should be monitored for poisoning symptoms and treatment should be supportive if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

<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 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 Tablet 50 mg and 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 Tablet 50 mg 50 mg, 100 mg and 40 mg 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 Tablet 50 mg and 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 Tablet 50 mg, 100 mg 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 Tablet 50 mg, 100 mg or lansoprazole 30 mg 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 Tablet 50 mg, 100 mg and 30 mg 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 Tablet 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 Tablet 50 mg and 30 mg lansoprazole with antibiotic combination therapy treatment groups, demonstrating non-inferiority.

5.2 Pharmacokinetic properties

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 (Cmax) 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 administration of 200 mg of oral tegoprazan 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).

Distribution

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

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 [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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

D-Mannitol, Microcrystalline cellulose, Croscarmellose sodium, Hydroxypropylcellulose, Colloidal silicon dioxide, Magnesium stearate, Opadry II pink (85F240134) [*PVA (Polyvinyl Alcohol), titanium Dioxide, PEG (polyethylene glycol), talc, iron oxide red*]

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C in the orginal package.

Keep out of the sight and reach of children.

If it is expired or is no longer needed, dispose of it safely.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Blister pack (Aluminium foil-Aluminium film) of 10 tablets. Paper box of 3 blister packs.

6.6 Special precautions for disposal <and other handling>

No special requirements

7. MARKETING AUTHORISATION HOLDER

Name & Address of Manufacturer:

HK inno.N Corporation

239, Osongsaengmyeong 2-ro Osong-eup, Heungdeok-gu Cheongju-si

Chungcheongbuk-do, Republic of Korea

Name & Address of Importer & Distributor:

POND'S CHEMICAL THAILAND R.O.P.

79 Ram-Indra Road, Anusawari, Bang Khen, Bangkok 10220, Thailand

Tel. (662) 900-5588 Fax (662) 552-1943

8. MARKETING AUTHORISATION NUMBER

Republic of Korea: 5147

Thailand Reg. No. : 1C xx/xx (NC)

9. DATE OF AUTHORISATION OF THE AUTHORISATION

Date of authorization (Republic of Korea) : 2018.07.05

Date of authorization (Thailand) : xx/xx/xxxx

10. DATE OF REVISION OF THE TEXT

5 OCTOBER 2023