Summary Product Characteristic for Pharmaceutical Product

1. Name of the medicinal product

Vonoprozan 20mg Tablet

2. Qualitative and quantitative composition

Each film coated tablet contains Vonoprazan Fumarate Eq. to Vonoprazan 20mg

Excipients with known effect:
Each Vonoprozan 20 mg Tablet contains 35.28 mg mannitol

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Light Brown to brown biconvex film coated tablet, plain on both sides.

4. Clinical particulars

4.1 Therapeutic indications

Vonoprazan is indicated for:

- Treatment of gastric ulcer (GU)
- Treatment of duodenal ulcer (DU)
- Treatment of reflux esophagitis (RE) (erosive esophagitis EE)
- Maintenance treatment of reflux esophagitis (erosive esophagitis)
- Prevention of recurrence of gastric ulcer or duodenal ulcer during NSAIDs administration.
- Adjunct to Helicobacter pylori eradication.

4.2 Posology and method of administration

Adults

Gastric ulcer
The usual dose is 20 mg of vonoprazan once a day. Administration should be limited to 8 weeks. Duodenal ulcer The usual dose is 20 mg of vonoprazan once a day. Administration should be limited to 6 weeks.
Reflux esophagitis (erosive esophagitis)
The usual dose is 20 mg of vonoprazan once a day. Administration should be limited to 4 weeks. However, when the effect is insufficient, treatment may be continued for up to 8weeks. In addition, for the maintenance of healing of reflux esophagitis in patients with repeat recurrence and relapse of the

condition, a dose of 10 mg is administered once a day; however, when the efficacy is inadequate, a dose of 20 mg may be administered once a day. The usual dose is 10 mg of vonoprazan once a day.

Adjunct to Helicobacter pylori eradication
When selecting antibacterial agents to be used in combination therapy, consideration should be given to official national, regional and local guidance regarding bacterial resistance, duration of treatment and appropriate use of the antibacterial agents. In a Phase III clinical study, the following 3 drugs were orally administered at the same time twice daily for 7 days: 20 mg vonoprazan, with amoxicillin hydrate and clarithromycin. When Helicobacter pylori eradication treatment with 3 drugs consisting of a proton pump inhibitor, amoxicillin hydrate, and clarithromycin fails, alternative treatment with the following 3 drugs is recommended; 20 mg vonoprazan, with amoxicillin hydrate and metronidazole, orally administered at the same time twice daily for 7 days. The doses of antibiotic should follow the respective label recommendations for H pylori eradication.

Method of Administration
Vonoprazan can be taken without regard to food or timing of food.

Special Patient Populations

Elderly Patients
Since the physiological functions such as hepatic or renal function are decreased in elderly patients in general, vonoprazan should be carefully administered.
Pediatric Patients
Vonoprazan has not been studied in patients under 18 years of age.

Impaired Renal Function
Vonoprazan should be administered with care in patients with renal disorders as a delay in the excretion of vonoprazan may occur, which may result in an increase in the concentration of vonoprazan in the blood.

Impaired Hepatic Function
Vonoprazan should be administered with care in patients with hepatic disorders as a delay in the metabolism and excretion of vonoprazan may occur, which may result in an increase in the concentration of vonoprazan in the blood.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hepatotoxicity
Hepatic function abnormalities including liver injury have been reported in clinical studies. Post marketing reports have also been received in patients treated with vonoprazan, many of which occurred shortly after initiation of treatment, Discontinuation of vonoprazan is recommended in patients who have evidence of liver function abnormalities or if they develop signs or symptoms suggestive of liver dysfunction.

Elevation of intragastric pH
Administration of vonoprazan results in elevation of intragastric pH and is therefore not recommended to be taken with drugs for which absorption is dependent on acidic intragastric pH.

Masking of Symptoms Associated with Gastric Malignancy
Gastric malignancy may present with symptoms associated with acid-related disorders which initially respond to drugs that elevate intragastric pH. A symptomatic response to vonoprazan does not exclude the presence of gastric malignancy.

Clostridium difficile, Serious colitis, including pseudomembranous colitis
There is an increased risk of gastrointestinal infection caused by Clostridium difficile as was reported in patients that received proton pump inhibitors. Drugs that elevate intragastric pH may be associated with an increased risk of Clostridium difficile gastrointestinal infection. Serious colitis accompanied with bloody stools, such as pseudomembranous colitis, may occur due to amoxicillin hydrate or clarithromycin being used for Helicobacter pylorieradication, in combination with vonoprazan. If abdominal pain and frequent diarrhea occur, appropriate measures, such as immediate discontinuation of the treatment, should be taken.

Benign gastric polyps
Benign gastric polyp has been observed in patient on long-term administration of PPIs.

Fractures
An increased risk for osteoporosis-related fractures of the hip, wrist or spine, predominantly in the elderly or in presence of other recognized risk factors,

has been reported in patients under treatment with proton pump inhibitors. The risk of fracture was especially increased in the patients receiving high dose or long term (a year or longer) treatment.

Hypomagnesemia
Severe hypomagnesaemia has been reported in patients on prolonged treatment with PPIs for at least three months and in most cases for a year.

4.5 Interaction with other medicinal products and other forms of interaction

Administration of vonoprazan results in elevation of intragastric pH, suggesting that it may interfere with the absorption of drugs where gastric pH is an important determinant of oral bioavailability. Use of vonoprazan is therefore not recommended with some of these drugs for which absorption is dependent on acidic intragastric pH such as atazanavir and nelfinavir, due to significant reduction in their bioavailability. Vonoprazan is metabolized mainly by hepatic drug-metabolizing enzyme CYP3A4 and partially by CYP2B6, CYP2C19 and CYP2D6. With strong CYP3A4 inhibitors, e.g., clarithromycin, blood concentration of vonoprazan may increase. It has been reported that blood concentration of vonoprazan increased in concomitant use with clarithromycin by 1.5-fold, but no dose adjustment of vonoprazan is considered necessary. Coadministration of vonoprazan with the antibiotic regimen clarithromycin and amoxicillinincreased concentrations of vonoprazan by up to 1.9-fold. No increase was observed with the antibiotic regimen of metronidazole and amoxicillin. No dose adjustment of vonoprazan isconsidered necessary.
There were no clinically significant effects of NSAIDs on the pharmacokinetics of vonoprazan, and no clinically significant effects of vonoprazan on the pharmacokinetics of NSAIDs.

4.6 Fertility, pregnancy and lactation

Pregnancy
No clinical studies have been conducted to date to evaluate vonoprazan in subjects who are pregnant. In a rat toxicology study, embryo-foetal toxicity was observed following exposure of more than approximately 28 times of the exposure (AUC) at the maximum clinical dose (40 mg/day) of vonoprazan. As a precaution, vonoprazan should not be administered to women who are or may be pregnant, unless the expected therapeutic benefit is thought to outweigh any possible risk.

Lactation

No clinical studies have been conducted to date to evaluate vonoprazan in subjects who are lactating. It is unknown whether vonoprazan is excreted in human milk. In animal studies it has been shown that vonoprazan was excreted in milk. During treatment with vonoprazan, nursing should be avoided if the administration of this drug is necessary for the mother.

4.7 Effects on ability to drive and use machines

The influence of vonoprazan on the ability to drive or use machines is unknown.

4.8 Undesirable effects

The following convention is used for the classification of the frequency of an adverse drug reaction (ADR) and is based on the Council for International Organizations of Medical Sciences (CIOMS) guidelines: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).
Clinical Trials: Clinical trial data for expected adverse events is based on pooled safety analysis from the following studies: EE healing (CCT-001 and CCT-002), EE maintenance therapy (CCT003 and OCT-001), GU healing (CCT-101), DU healing (CCT-102), prevention of recurrence of peptic ulcer associated with NSAID use (CCT-301, OCT-301 and OCT-303) and treatment of nonerosive reflux disease (NERD; CCT-201). Although the study in patients with NERD has the placebo arm and is considered as the best data, the number of patients (N=449 and 278 for TAK-438 and placebo, respectively) is relatively small compared to the number of patients of all other activecomparator studies combined (N=3162 and 1392 for TAK-438 and AG-1749 [Lansoprazole], respectively). Therefore, the pooled safety data of active-comparator studies are used for the primary analysis. The safety data of CCT-201 study are analyzed separately. (Note: AG-1749 (Lansoprazole) is the only comparator used in the comparator studies.)

Adverse reactions with Vonoprazan in clinical studies				
Frequency/System organ Class	Very common	Common	Uncommon	Rare
Gastrointestinal disorders	-	Diarrhea Constipation	Nausea Abdominal distension	-
Investigations	-	-	Gamma-glutamyl transferase increased AST increased liver function test abnormal ALT increased.	-

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

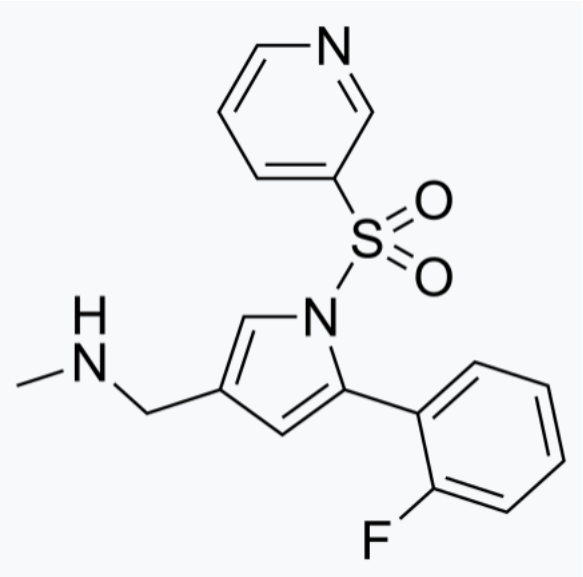
There is no experience of overdose with vonoprazan. Vonoprazan is not removed from the circulation by hemodialysis. If overdose occurs, treatment should be symptomatic and supportive.

5. Pharmacological properties

5.1 pharmacodynamic properties

Pharmacotherapeutic group: Potassium competitive acid blocker (PCAB)
ATC code: A02BC08

Vonoprazan is a potassium competitive acid blocker (PCAB) and inhibits H+, K+-ATPase in a reversible and potassium-competitive manner. It does not require activation by acid. Vonoprazan is a strong base with a high affinity for the acid pump of gastric cells inhibiting gastric acid production. The chemical formula is C21H20FN3O6S and the chemical structure is:



Vonoprazan exerts a strong inhibitory effect on formation of mucosal damage in upper part of the gastrointestinal tract. Vonoprazan does not exhibit anti-Helicobacter pylori activity nor inhibitory activity against Helicobacter pylori ureas. Inhibiting activity on gastric acid secretion: Following consecutive administration of Vonoprazan at a dose of 10mg or 20mg in healthy adult

male subjects for 7 days, proportions of the time exhibiting gastric pH of 4 or above within 24 hours were 63±9% and 83±17%, respectively.

Pharmacodynamic effects

Mechanism of Action:
Vonoprazan does not require activation by acid and inhibits H+, K+-ATPase in a reversible and potassium-competitive manner. Vonoprazan has a strong basicity and resides on the acid production site of gastric parietal cells for a long time, thereby inhibiting gastric acid production. Vonoprazan exerts a strong inhibitory effect on formation of mucosal damage in upper part of the gastrointestinal tract. Vonoprazan does not exhibit anti-Helicobacter pylori activity nor inhibitory activity against Helicobacter pylori ureas.
Inhibiting activity on gastric acid secretion: Following consecutive administration of Vonoprazan at a dose of 10mg or 20mg in healthy adult male subjects for 7 days, proportions of the time exhibiting gastric pH of 4 or above within 24 hours were 63±9% and 83±17%, respectively. Adjunctive effect on eradication of Helicobacter pylori: The role of Vonoprazan in the Helicobacter pylori eradication is considered to increase intragastric pH leading to the enhancement of antibacterial activity of amoxicillin hydrate, clarithromycin and metronidazole which are concomitantly administered.

5.2 Pharmacokinetic properties

Absorption:
Effect of Foods: The following table shows pharmacokinetic parameters of Vonoprazan following single administration of Vonoprazan to healthy adult male subjects at 20mg under fasting and after meal. Effect of food on pharmacokinetic was little observed. (See Table 1) Pharmacokinetics parameters at 20 mg single administration under fasting and after meal (healthy male adults).

Dose Condition	**Under fasting**	**After meal**
Tmax (h)	1.5 (1.0,3.0)	3.0 (1.0, 4.0)
Cmax (ng/ml)	24.3 ± 6.6	26.8 ± 9.6
T1/2 (h)	7.7 ± 1.0	7.7 ± 1.2
AUC 0-48 (ng*h/ml	222.1 ± 69.7	238.3 ± 71.1

Mean ± SD of 12 subjects [Tmax is expressed by median (minimum value, maximum value)]

Pharmacokinetics at consecutive administration: At consecutive administration of a daily dose of 10mg or 20mg of Vonoprazan in healthy adult male subjects once daily for 7 days, AUC(0-tau) and Cmax increase as the dose increases. The degree of these increases is slightly higher than the dose ratio. It is considered that the steady state has been reached by day 3 of administration, since the trough level of the blood concentration of Vonoprazan is constant between day 3 and day 7 of administration. In addition, it is considered that pharmacokinetics of Vonoprazan at consecutive

administration may not be time-dependent, as the result of the evaluation of accumulation with regard to AUC(0-tau) and T1/2 of Vonoprazan. The following table shows pharmacokinetic parameters of Vonoprazan on day 7 of administration. Pharmacokinetics parameters at 10mg or 20mg consecutive administration (healthy male adults).

Dose	**10mg**	**20 mg**
Tmax (h)	1.5(0.75, 3.0)	1.5 (0.75, 3.0)
Cmax (ng/ml)	12.0 ± 1.8	23.3 ± 6.6
T1/2 (h)	7.0 ± 1.6	6.1 ± 1.2
AUC 0-48 (ng*h/ml	79.5 ± 16.1	151.6 ± 40.3

Mean± S.D of 9 subjects [Tmax is expressed by the median (minimum value, maximum value)

Distribution:

Protein binding rate: The protein binding rate is 85.2 to 88.0% when [14C] Vonoprazan in the range of 0.1 to 10µg/mL is added to human plasma (in vitro).

Metabolism:

Vonoprazan is metabolized mainly by hepatic drug-metabolizing enzyme CYP3A4 and partially by CYP2B6, CYP2C19 and CYP2D6. Vonoprazan is also metabolized by sulfotransferase SULT2A1 (in vitro). Vonoprazan exhibits time-dependent inhibitory effect on CYP2B6, CYP2C19 and CYP3A4/5 (in vitro). In addition, Vonoprazan shows a slight concentration-dependent inductive effect on CYP1A2, but it shows little inductive effect on CYP2B6 and CYP3A4/5 (in vitro).

Excretion:

When radioactive-labeled drug (15mg as Vonoprazan) is orally administered to non-Japanese healthy adult male subjects, 98.5% of the radioactivity administered is excreted into urine and feces by 168 hours after administration: 67.4% into urine and 31.1% into feces.

Patients with Specific Backgrounds:

Pharmacokinetics in patients with hepatic disorders: The clinical trial conducted in abroad to evaluate the effect of hepatic disorders or pharmacokinetics in subjects with normal hepatic function and patients with mild (Child-Pugh score: A), moderate (Child-Pugh score: B), and severe (ChildPugh score: C) hepatic disorder when administered with the drug as Vonoprazan 20mg shows that AUC(0-inf) and Cmax were higher by 1.2 to 2.6 times and 1.2 to 1.8 times, respectively, in patient with mild, moderate and severe hepatic disorder, compared to subjects with normal hepatic function.

Pharmacokinetics in patients with renal disorders: The clinical trial conducted in abroad to evaluate the effect of renal disorders on pharmacokinetics of Vonoprazan in subjects with normal renal function (eGFR: ≥90mL/min/1.73m^2), patients with mild (eGFR: 60-89mL/min/1.73m^2), moderate (eGFR: 30-59mL/min/1.73m^2), and severe

(eGFR: 15-29mL/min/1.73m2) renal disorder and patients with end-stage renal disease (ESRD) (eGFR: <15mL/min/1.73m2) when administered the drug as Vonoprazan 20mg shows that AUC(0-inf) and Cmax were higher by 1.3 to 2.4 times and 1.2 to 1.8 times, respectively, in patients with mild, moderate and severe renal disorder compared to subjects with normal renal function. AUC(0-inf) and Cmax were higher by 1.3 times and 1.2 times, respectively, in ESRD patients compared to those in subjects with normal renal function.

5.3 Preclinical safety data

Single-Dose Toxicity

Single-dose oral administration of vonoprazan in rodent and non-rodent species:

● Rat MNLD: 200 mg/kg.

● Dog MNLD: 10 mg/kg.

Repeated-Dose Toxicity

Repeated-dose oral administration of vonoprazan in rats (up to 26 weeks) and dogs (up to 39 weeks):

● For rats: The NOAEL was 5 mg/kg/day (0.46 and 0.43 × MRHD for Japanese and British, respectively) in males and 10 mg/kg/day (3.5 and 3.3 × MRHD for Japanese and British, respectively) in females, determined by the 26-week study, and the observations resulted from pharmacological action of vonoprazan.

● For dogs: The NOAEL was 0.6 mg/kg/day (0.91 and 0.85 × MRHD for Japanese and British, respectively) in males and 0.6 mg/kg/day (0.75 and 0.71 × MRHD for Japanese and British, respectively) in females, determined by the 39-week study, and the observation resulted from pharmacological action of vonoprazan.

Safety Pharmacology

Safety pharmacology study was not conducted or required to support the proposed indication

Genotoxicity No genetic risk was found in a standard battery of genotoxicity studies.

Reproductive and Developmental Toxicity

Fertility and early embryonic development in rats:

● The NOAEL was ≥300 mg/kg/day for both males and females. Embryonic fetal development in rats and rabbits:

● The NOAELs for maternal was 30 mg/kg/day in rats and 3 mg/kg/day in rabbits. The NOAELs for fetus was 100 mg/kg/day in rats and >30 mg/kg/day in rabbits. Pre- and postnatal developments in rats:

● The NOAEL was determined as 10 mg/kg/day for F0 and F1 in rats.

Carcinogenicity

Increased incidence of tumor was found in liver and stomach in 2-year mouse and rat tests.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core:
Mannitol
Micro-crystalline Cellulose PH 101
Hydroxy Propyl Cellulose
Croscarmellose Sodium
Polyvinyl pyrrolidone K30
Fumaric acid
Magnesium stearate
Micro-crystalline Cellulose PH 102
Colloidal Anhydrous silica (Aerosil)
Purified water

Coat:
Ready coat film aq. Brown
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Blister pack of printed Aluminium-Aluminium Foil packed in printed carton along with leaflet.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed in accordance with local requirements.

7. Marketing authorisation holder and manufacturing site addresses

Marketing authorisation holder

Harley's Limited
63 Westlands Rd,
Nairobi, Kenya.

Manufacturing Site Addresses

Cubit Lifesciences Llp.,
Plot No. 39-40, Ozone Industrial park,
At & post Kerala-Bhayla, Near Kerala GIDC, Taluka:
Bavla, Ahmedabad, India.

8. Marketing authorisation number(s)

H2024/CTD10599/24228

9. Date of first authorisation/renewal of the authorisation

Date of first authorization: 28-Mar-2024

10. Date of revision of the text

Nov-2024