Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Vonoprazan 20 mg film-coated tablets

2. Qualitative and quantitative composition

Each film-coated tablet contains 26.72mg of Vonoprazan Fumarate
Excipients with known effects
Mannitol BP 35.28mg
For a full list of excipients, see section 6.1

3. Pharmaceutical form

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

4. Clinical particulars

4.1 Therapeutic indications

Vonoprazan is indicated for:
Gastric ulcer, duodenal ulcer, reflux esophagitis, prevention of recurrence of gastric or duodenal ulcer during low-dose aspirin administration, prevention of recurrence of gastric or duodenal ulcer during non-steroidal anti-inflammatory drug (NSAID) administration.
In combination with amoxicillin and clarithromycin for the treatment of Helicobacter pylori (H.pylori) infection in adults.
In combination with amoxicillin for the treatment of H. pylori infection in adults.

4.2 Posology and method of administration

Reflux oesophagitis
Adult: 20 mg once daily for 4 weeks, may be followed by a further 4 weeks if necessary.
Maintenance therapy for healing in patients with repeated recurrence.

Gastric ulcer and duodenal ulcer
The usual adult dosage for oral use is 20mg of Vonoprazan
Administered orally once daily, an 8-week treatment for gastric ulcer and a 6-week treatment for duodenal ulcer.

Prevention of recurrence of gastric or duodenal ulcer during low-dose aspirin administration
The usual adult dosage is one tablet of 10mg of Vonoprazan administered orally once daily.

Prevention of recurrence of gastric or duodenal ulcer during Non-Steroidal Anti-inflammatory drug (NSAID) administration
The usual adult dosage is one tablet of 10mg of Vonoprazan administered orally once daily.

Treatment of *H.pylori* Infection

• Triple Therapy: The recommended adult oral dosage is vonoprazan 20 mg plus amoxicillin 1,000 mg plus clarithromycin 500 mg, each given twice daily (in the morning and evening, 12 hours apart) for 14 days.

• Dual Therapy: The recommended adult oral dose is vonoprazan 20 mg given twice daily (in the morning and evening) plus amoxicillin 1,000 mg three times daily (in the morning, mid-day, and evening) for 14 days.
• Also refer to the amoxicillin and clarithromycin full prescribing information.

Method of Administration:
Vonoprazan can be taken without regard to food or timing of food.
It should only be taken with a glass of water. Do not crush or chew.
For missed doses:
For the healing or maintenance of healed erosive esophagitis: If a dose is missed, administer vonoprazan as soon as possible within 12 hours after the missed dose. If more than 12 hours have passed, skip the missed dose and administer the next dose at the regularly scheduled time.
For the treatment of H. pylori infection: If a dose is missed, administer vonoprazan as soon as possible within 4 hours after the missed dose. If more than 4 hours have passed, skip the missed dose and administer the next dose at the regularly scheduled time. Continue the normal dosing schedule until the treatment is completed.

4.3 Contraindications

Vonaprazan in contraindicated in:
• Patients with hypersensitivity to Vonoprazan or any excipient of the product.
• Patients receiving atazanavir sulphate, nelfinavir or rilpivirine hydrochloride.

4.4 Special warnings and precautions for use

General
At the treatment, the course of the disease should be closely observed, and the minimum therapeutic necessity should be used according to the disease condition.
In the long term, treatment with Vonoprazan, close observation by such means as endoscopy should be made.
In the maintenance of healing of reflux esophagitis, Vonoprazan should be administered only to patients who have repeated recurrence and recrudescence of the condition.
Administration to the patients who do not necessitate maintenance of healing should be avoided.
When the healing is maintained over a long period and when there is no risk of recurrence, the dose reduction to a dose of 10mg from a dose of 20mg, or suspension of administration, should be considered.

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.

Acute Tubulointerstitial Nephritis
Discontinue treatment and evaluate patients.

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. Hepatic function abnormalities including liver injury have been reported. 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.

Masking the symptoms associated with Gastric Malignancy
In adults, symptomatic response to therapy with vonoprazan does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing in patients who have a suboptimal response or an early symptomatic relapse after completing treatment with vonoprazan. In older patients, also consider endoscopy.

Clostridioides difficile-Associated Diarrhea (CDAD)
May be associated with an increased risk; use the shortest duration of treatment appropriate to the condition.

Bone Fracture, including Osteoporosis-related Fracture
Use the shortest duration of treatment appropriate to the condition.

Severe Cutaneous Adverse Reactions
Discontinue at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

Vitamin B12 (Cobalamin) Deficiency
Long-term use may lead to malabsorption or deficiency; consider further workup if clinical symptoms are present.

Hypomagnesemia and Mineral Metabolism
Consider monitoring magnesium levels before starting treatment and periodically if prolonged treatment is expected, or if concomitant use of digoxin or other drugs that cause hypomagnesemia.

Interactions with Investigations for Neuroendocrine Tumors
Increased chromogranin A (CgA) levels may interfere with diagnostic investigations; temporarily stop vonoprazan at least 14 days before assessing CgA levels.

Fundic Gland Polyps
Risk increases with long-term use; use the shortest duration of

treatment appropriate to the condition.

Use in pregnancy
Vonoprazan should be used in pregnant women or women suspected of pregnancy only if the expected therapeutic benefit is thought to outweigh any possible risk.

Use during lactation
Because of the potential risk of adverse liver effects shown in animal studies with vonoprazan, it is advisable to avoid the administration of Vonoprazan to nursing mothers. However, when the administration is indispensable, nursing should be discontinued.

Use in children
Vonoprazan has not been studied in patients under 18 years of age.

Use in the Elderly
Since the physiological functions, such as hepatic or renal function, are decreased in elderly patients in general, vonoprazan should be carefully administered.

4.5 Interaction with other medicinal products and other forms of interaction

Administration of vonoprazan results in elevation of intra-gastric 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 intra-gastric pH, such as atazanavir and nelfinavir, due to a 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, the blood concentration of vonoprazan may increase. It habeen reported that the 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 amoxicillin increased 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 is considered 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.

Co-administration of midazolam (a sensitive CYP3A4 substrate) with multiple doses of vonoprazan increased the concentration of midazolam by 1.9-fold in healthy subjects. Caution is advised when vonoprazan is co-administered with other sensitive CYP3A4 substrates, notably those having a narrow therapeutic index.

4.6 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 lactating subjects. 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 the ability to drive and use machines

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.

4.8 Undesirable effects

Serious adverse reactions include: Acute Tubulointerstitial Nephritis, Clostridioides difficile-Associated Diarrhea, bone fractures, Severe Cutaneous Adverse Reactions, vitamin B12 (Cobalamin) deficiency, hypomagnesemia, and mineral metabolism, and fundic gland polyps.

The most commonly reported adverse drug reactions, during controlled clinical trials with rabeprazole, were headache, diarrhea, abdominal pain, asthenia, flatulence, rash, and dry mouth.

The majority of adverse events experienced during clinical studies were mild or moderate in severity and transient in nature.

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 (P-CAB) - antibiotics
ATC code: A02BC08.
Mechanism of action
Vonoprazan is a potassium competitive acid blocker (P-CAB) and does not require activation by acid. It 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 does not require activation by acid. Vonoprazan may selectively concentrate in the parietal cells in both the resting and stimulated states. Vonoprazan binds to the active pumps in a noncovalent and reversible manner. This drug exerts a strong inhibitory effect on the formation of mucosal damage in the upper part of the gastrointestinal tract. Vonoprazan does not exhibit anti-Helicobacter pylori activity nor inhibitory activity against Helicobacter pylori urease.
Adjunctive effect on the eradication of Helicobacter pylori: The role of Vonoprazan in the Helicobacter pylori eradication is considered to increase intra-gastric pH, leading to the enhancement of antibacterial activity of amoxicillin hydrate, clarithromycin, and metronidazole, which are concomitantly administered.

Antisecretory Activity
Following a single 10 mg or 20 mg dose of vonoprazan, the onset of the anti-secretory effect as measured by intra-gastric pH occurs within 2 to 3 hours. The elevated intra-gastric pH levels compared to placebo increase with dose and are maintained for over 24 hours after dosing. The inhibitory effect of vonoprazan on acid secretion increases with repeated daily dosing, and steady state is achieved by Day 4. The antisecretory effect of vonoprazan decreases following drug discontinuation, although intragastric pH remained elevated compared to placebo for 24 to 48 hours following the dose on Day 7.

Serum Gastrin Effects
The effect of vonoprazan on serum gastrin concentrations was evaluated in 514 patients for up to 8 weeks (healing phase) and in 592 patients for up to 6 months (maintenance phase). During the healing phase, the mean fasting gastrin levels at Week 2 increased from baseline after treatment with vonoprazan 20 mg, and levels were similar at Week 2 and Week 8. In the 6-month maintenance phase, the mean gastrin levels remained elevated with vonoprazan 20 mg and the mean serum gastrin levels returned to normal within 4 weeks of discontinuation of treatment.

Increased gastrin causes enterochromaffin-like cell hyperplasia and increased serum CgA levels. The increased CgA levels may cause false-positive results in diagnostic investigations for neuroendocrine Tumours.

Enterochromaffin-Like Cell (ECL) Effects
Human gastric biopsy specimens were obtained from 135 patients treated with vonoprazan 20 mg once daily for up to 260 weeks. An increase in the incidence of hyperplasia of the parietal cells
and G-cells was observed, which is consistent with the pharmacological action of a potassium-competitive acid blocker. No neoplastic changes were observed.

Cardiac Electrophysiology
At a single dose of 120 mg (6 times the maximum recommended dose), vonoprazan does not prolong the QT interval to any clinically relevant extent.

5.2 Pharmacokinetic properties

Pharmacokinetics at consecutive administration of a daily dose of 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 the pharmacokinetics of Vonoprazan at consecutive administration may not be time-dependent, as a result of the evaluation of accumulation with regard to AUC (0-tau) and T1/2 of Vonoprazan.

Dose condition	**20mg**
Tmax (h)	1.5 (0.75, 3.0)
Cmax (ng/ml)	26.3 ± 6.6
T1/2 (h)	6.1 ± 1.2
AUC(0-tau) (ng.h/ml)	151.6 ± 40.3

Absorption
Absolute bioavailability has not been determined. The pharmacokinetic parameters of Vonoprazan following a single administration of Vonoprazan to healthy adult male subjects
at 20mg under fasting and fed conditions are presented in the table below.

Tmax (h)	Under fasting	After meal
Tmax (h)	1.5 (0.75, 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-tau) (ng.h/ml)	222.1 ± 69.7	238.3 ± 71.1

Distribution

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 a 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).

Elimination

When radioactive-labelled drug (15mg as Vonoprazan) is orally administered to 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.

Special Populations

Patients with renal impairment

The effect of renal disorders on the pharmacokinetics of Vonoprazan in subjects with normal renal function, patients with mild, moderate, and severe renal disorders, and patients with end-stage renal disease (ESRD) when administered the drug as a single dose of Vonoprazan 20mg shows that AUC∞ 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, showing an increase with a reduction in renal function. AUC∞ 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.

Patients with hepatic impairment

The effect of hepatic disorders on pharmacokinetics in subjects with normal hepatic function and patients with mild, moderate, and severe hepatic disorders when administered the drug as a

single dose of Vonoprazan 20mg shows that AUC∞ and Cmax were higher by 1.2 to 2.6 times and 1.2 to 1.8 times, respectively, in patients with mild, moderate and severe hepatic disorder, compared to subjects with normal hepatic function.

5.3 Preclinical safety data

Carcinogenesis

Vonoprazan was non-carcinogenic in a long term carcinogenicity study in mice when administered the drug daily via oral gavage for up to 2 years at 6, 20, 60, and 200 mg/kg/day.

Treatment-related tumors, related to exaggerated pharmacology or sepsis-specificity, were noted in the stomach and liver. In the stomach, benign and malignant neuroendocrine cell tumors were observed at ≥20 (males) and ≥60 (females) mg/kg/day and ≥6 (males) and ≥60 (females) mg/kg/day, respectively. In the liver, increased incidences of hepatocellular adenoma and carcinoma were observed at ≥20 (males) and ≥60 (females) mg/kg/day, and at ≥60 (males) and 200 (females) mg/kg/day, respectively. Hyperplasia of the neuroendocrine cells and associated tumors in the stomach may be due to hypergastrinemia as a consequence of inhibiting gastric acid secretion. The hepatocellular tumors are likely rodent-specific findings that are attributed to prolonged induction of hepatic drug-metabolizing enzymes.

Vonoprazan was non-carcinogenic in a long-term carcinogenicity study in rats administered the drug via oral gavage at 5, 15, 50, and 150 mg/kg/day. Treatment-related tumors, related to exaggerated pharmacology or species-specificity, were noted in the stomach and liver. In the stomach, benign and malignant neuroendocrine cell tumors were observed at ≥5 mg/kg/day, except for malignant neuroendocrine tumor at 50 mg/kg/day (males). In some instances, in benign and malignant neuroendocrine cell tumors, tumor cells showed eosinophilic change but these tumors were also judged to be of neuroendocrine cell origin. In the liver, increased incidences of hepatocellular adenoma and carcinoma were observed at ≥50 mg/kg/day except for hepatocellular carcinoma at 50 mg/kg/day (females). Tumor findings in the stomach and liver are believed to be due to hypergastrinemia as a consequence of inhibiting gastric acid secretion and rodent-specific induction of hepatic drug-metabolizing enzymes, respectively.

The occurrence of 4 hepatocholangiocellular tumors at ≥50 mg/kg/day (males) were considered to be treatment related because they were considered to be associated with induction of hepatocellular tumor, but pairwise comparison did not demonstrate a statistically significant effect.

Mutagenicity

Vonoprazan did not exhibit any mutagenic or clastogenic activity in the in vitro Ames assay, in vitro mammalian chromosome aberration assay,

and in vivo rat micronucleus assay.

Impairment of Fertility

When administered daily via oral gavage to male and female rats, there were no effects on sperm analysis, estrous cycles or number of corpora lutea observed at doses up to 300 mg/kg/dose. Males were administered vonoprazan before and during mating and females dosed for 2 weeks pre-mating through Gestation Day (GD) 6. The NOAEL for male and female general toxicity was 30 mg/kg/day and ≥300 mg/kg/day for reproductive function and early embryonic development.

6. Pharmaceutical Particulars

6.1 List of Excipients

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)
Ready coat aq. Brown
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

36 months.

6.4 Special Precautions for Storage

Store below 30°C. Protect from light and moisture.

6.5 Nature and Content of Container

2 X 10 Alu.Alu Tablets

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of per local requirements.

7. Marketing Authorization Holder

Harley's Limited

63 Westlands Rd, Nairobi,

Country: Kenya.

8. Marketing Authorization Number
CTD10599

9. Date of first authorization/renewal of the authorization
28/03/2024

10. Date of revision of the text
5/5/2025