Voniza®

Vonoprazan

COMPOSITION
Voniza® 10: Each film coated tablet contains Vonoprazan Fumarate INN equivalent to 10 mg of Vonoprazan.
Voniza® 20: Each film coated tablet contains Vonoprazan Fumarate INN equivalent to 20 mg of Vonoprazan.

PHARMACOLOGY

Pharmacodynamic properties
Pharmacotherapeutic group: Drugs for acid related disorders/ Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)/Proton pump inhibitor ATC Code: A02BC08.

Vonoprazan is a potassium-competitive acid blocker used in the treatment of acid-related disorders and as an adjunct to Helicobacter pylori eradication.

- 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.
- Adjunct to Helicobacter pylori eradication in the following settings: Gastric ulcer, duodenal ulcer, gastric mucosa-associated lymphatic tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, the stomach after endoscopic resection of early stage gastric cancer or Helicobacter pylori gastritis.

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 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 urease.
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.

Pharmacodynamic effects
The use of vonoprazan leads to an increase in intragastric pH. The inhibitory effect of vonoprazan on acid secretion increases with repeated daily dosing. Although the antisecretory effect of vonoprazan decreases after drug discontinuation, intragastric pH remains elevated for 24 to 48 hours. Vonoprazan does not have a clinically significant effect on QT prolongation. Compared to other potassium-competitive acid blockers (PCABs), vonoprazan has a higher point-positive charge (pKa of 9.06). This allows vonoprazan to accumulate at higher concentrations in the canalicular space of the gastric parietal cells, where it binds H+, K+-ATPase in a K+-competitive and reversible manner. Compared to other PCABs, such as SCH28080, or proton-pump inhibitors, such as lansoprazole, vonoprazan has a more potent H+, K+-ATPase inhibitory activity.

Pharmacokinetics
Pharmacokinetics 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.

Absorption
Vonoprazan has time-independent pharmacokinetics, and steady-state concentrations are reached after 3 to 4 days. In patients given a single dose of vonoprazan, the AUC0-12h, Cmax and Tmax were 154.8 nghr/mL, 25.2 ng/mL, and 2.5 h. In patients given vonoprazan twice daily, the AUC0-12h, Cmax and Tmax were 272.5 nghr/mL, 37.8 ng/mL, and 3.0 h.5 In patients given 10 mg to 40 mg of vonoprazan daily for 7 days, the AUC and Cmax increased in a dose-proportional manner. In healthy subjects given 20 mg of vonoprazan, a high-fat meal led to a 5% and 15% increase in Cmax and AUC; however, these changes were not considered clinically significant.

Distribution
The protein binding rate 85.2 to 88.0% when [14C] Vonoprazan in the range of 0.1 to 10 μg/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 bysulfotransferase 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).

Protein binding
In healthy subjects, the plasma protein binding of vonoprazan ranges from 85% to 88%. At plasma concentrations between 0.1 and 10 mcg/mL, the plasma protein binding of vonoprazan is independent of concentration.

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 patient populations
Patients with renal impairment:
The effect of renal disorders on pharmacokinetics of Vonoprazan in subjects with normal renal function, patients with mild, moderate, and severe renal disorder 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 disorder 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.

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

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

INDICATIONS/USES

- Gastric ulcer (GU)
- Duodenal ulcer (DU)
- Reflux esophagitis (RE) and (erosive esophagitis EE)
- Maintenance treatment of reflux esophagitis (erosive esophagitis) in patients with repeat recurrence and relapse of the condition
- Prevention of recurrence of gastric ulcer or duodenal ulcer during NSAIDs administration
- Adjunct to Helicobacter pylori eradication associated with: Gastric ulcer, duodenal ulcer, gastric MALT lymphoma, idiopathic thrombocyto penic purpura, the stomach after endoscopic resection of early stage cancer, or Helicobacter pylori gastritis

DOSAGE
Posology and method of administration
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.

Reflux esophagitis: The usual adult dose for oral use is 20mg of Vonoprazan administered once daily for a total of 4 weeks of treatment. If that dosing proves insufficient, the administration should be extended, but for no longer than 8 weeks of treatment. For the maintenance therapy of reflux esophagitis showing recurrence and recrudescence, the dose for oral use is 10mg of Vonoprazan once daily. However, when the efficacy is inadequate, the dosage may be increase up to 20mg of Vonoprazan once daily.

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.

Adjunct to Helicobacter pylori eradication: For adults, the following three-drug regimen should be administered orally at the same time twice daily for seven days: 20mg of Vonoprazan, 750mg of amoxicillin hydrate and 200mg of clarithromycin. The dose of clarithromycin may be increased as clinically warranted. However, dosage should not exceed 400mg twice daily.

If Helicobacter pylori eradication with a three-drug regimen comprising a proton pump inhibitor, amoxicillin hydrate and clarithromycin has been unsuccessful, as an alternative treatment, adults should be administered the following three drugs orally twice daily for seven days: 20mg of Vonoprazan, 750mg of amoxicillin hydrate and 250 mg of metronidazole.

Indication	*Dose*	*Frequency*
Gastric ulcer	20 mg	Once daily for 8 weeks
Duodenal ulcer	20 mg	Once daily for 6 weeks
Reflux esophagitis (erosive esophagitis):	20 mg	Once daily for 4 weeks
Prevention of recurrence of gastric ulcer or duodenal ulcer during NSAIDs administration	10 mg	Once a day

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

SIDE EFFECTS
Following adverse reactions have been reported with the use of Vonoprazan: Diarrhea, constipation, drug hypersensitivity (including anaphylactic shock), drug eruption, urticaria, hepatotoxicity, jaundice, rash, nausea, abdominal distension, gamma-glutamyl transferase increased, AST increased, Liver function test abnormal, ALT increased, ALP increased, LDH increased, edema and eosinophilia.

PRECLINICAL SAFETY DATA
Overdose with vonoprazan has not been reported. No serious adverse reactions were observed during clinical studies in subjects given a single dose of 120 mg of vonoprazan. Vonoprazan is not removed from the circulation by hemodialysis. In case of overdose, the FDA label for Vonoprazan Triple Pak and Vonoprazan Dual Pak recommends symptomatic and supportive treatment. Animal studies evaluating vonoprazan mutagenicity (Ames test) have reported negative results. No effects on fertility and reproductive performance were observed in rats given 300 mg/kg/day of vonoprazan orally (133, the maximum recommended human dose). Mice given 6, 20, 60 and 200 mg/kg/day of vonoprazan orally (0.4, 4, 19, and 93 times the maximum recommended human dose) developed hyperplasia of neuroendocrine cells, gastropathy and benign and/or malignant neuroendocrine cell tumors (carcinoids) in the stomach.

CONTRAINDICATIONS
Vonoprazan is contraindicated in: Patients with hypersensitivity to Vonoprazan or to any excipient of the product. Patients receiving atazanavir sulphate, nelfinavir or rilpivirine hydrochloride. Hypersensitivity to the active ingredients or to any of the excipients.

PRECAUTIONS
General
At the treatment, the course of the disease should closely be 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 the patients who repeat 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 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.

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.

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. Symptomatic response to Vonoprazan does not preclude the presence of gastric malignancy. It is therefore, necessary to ascertain the ulcer is not of a malignant nature before initiating the administration of this drug.
For prevention of recurrent gastric or duodenal ulcer associated with low-dose aspirin administration Vonoprazan should be administered to patients who continue receiving low-dose aspirin to prevent Thrombogenesis/embolization. A medical history of gastric or duodenal ulcer should be checked before starting administration of vonoprazan.

USE IN PREGNANCY & LACTATION
Pregnancy: No clinical studies have been conducted to date to evaluate vonoprazan in subjects who are pregnant. In a rat toxicology study, embryo-fetal 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 bene-t 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.

Effects on ability to drive and use machines
Vonoprazan should not affect your ability to drive or operate machinery. However, be cautious about the side effects that may affect your reaction time and focus.

STORAGE
Store below 30°C in a dry place. Keep all medicine out of reach of children.

HOW SUPPLIED
Voniza® 10: Each box contains 30 tablets in a blister pack.
Voniza® 20: Each box contains 30 tablets in a blister pack.

Manufactured by :
SQUARE PHARMACEUTICALS
KENYA EPZ LTD.
Athi River, Machakos, Kenya

SQUARE