SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vonotec (Vonoprazan) 20mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Vonoprazan.....20mg

(As Vonoprazan Fumarate)

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pink colored oval shaped biconvex film coated tablet, embossing "20" on one side and bisect line on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vonotec (Vonoprazan) is indicated for:

- Treatment of gastric ulcer, duodenal ulcer, or reflux esophagitis; prevention of recurrent gastric or duodenal ulcer associated with low-dose aspirin administration, and prevention of recurrent gastric or duodenal ulcer associated with non-steroidal anti-inflammatory drug administration.
- Adjunct therapy to Helicobacter pylori eradication in the following: Gastric or 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.

4.2 Posology and method of administration

DOSAGE AND ADMINISTRATION

Treatment of gastric ulcer and duodenal ulcer

The usual adult dosage is 20 mg of Vonotec (Vonoprazan) administered orally once daily. The usual treatment period should be up to 8 weeks for gastric ulcer and up to 6 weeks for duodenal ulcer.

Treatment of reflux esophagitis

The usual adult dosage is 20 mg of Vonotec (Vonoprazan) administered orally once daily. The usual treatment period should be up to 4 weeks, but it may be extended up to 8 weeks if response to the initial course of the treatment is inadequate.

For the maintenance therapy to prevent recurrence or relapse of reflux esophagitis, the dosage is 10 mg administered orally once daily. However, when response to the initial dose is inadequate, the dose may be increased to 20 mg once daily.

Prevention of recurrent gastric or duodenal ulcer associated with low-dose aspirin administration

The usual adult dosage is 10 mg of Vonotec (Vonoprazan) administered orally once daily.

Prevention of recurrent gastric or duodenal ulcer associated with non-steroidal anti-inflammatory drug administration

The usual adult dosage is 10 mg of Vonotec (Vonoprazan) administered orally once daily.

Adjunct therapy to Helicobacter pylori eradication

For adults, the following 3-drug regimen should be administered orally at the same time twice daily for 7 days: 20 mg of Vonotec (Vonoprazan), 750 mg (potency) of amoxicillin hydrate, and 200 mg (potency) of clarithromycin. The dose of clarithromycin may be increased as clinically warranted, but it should not exceed 400 mg (potency)/dose twice daily.

In adult patients in whom Helicobacter pylori eradication with a 3-drug regimen comprising a proton pump inhibitor, amoxicillin hydrate, and clarithromycin was unsuccessful, the following 3 drugs should be administered orally twice daily for 7 days as an alternative treatment: 20 mg of Vonotec (Vonoprazan), 750 mg (potency) of amoxicillin hydrate, and 250 mg of metronidazole.

4.3 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.

4.4 Special warnings and precautions for use

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.

For prevention of recurrent gastric or duodenal ulcer associated with non-steroidal anti-inflammatory drug administration

Vonoprazan should be administered to patients who continue receiving NSAID to control pain associated with rheumatoid arthritis, osteoarthritis, etc. A medical history of gastric or duodenal ulcer should be checked before starting administration of vonoprazan.

For adjunct therapy to Helicobacter pylori eradication

1. The efficacy of Helicobacter pylori eradication in patients with advanced gastric MALT lymphoma has not been established.

2. For patients with idiopathic thrombocytopenic purpura, the Helicobacter pylori eradication should be performed only in patients who are considered eligible for the eradication therapy in light of the guideline, etc.

3. The efficacy of the Helicobacter pylori eradication for treatment of the stomach after endoscopic resection of early stage gastric cancer has been established, but not for other therapies for prevention of gastric cancer development.

4. Before vonoprazan is administered to patients with Helicobacter pylori gastritis, the patients should be checked that they are Helicobacter pylori positive and endoscopically that they are affected by Helicobacter pylori gastritis.

Impaired Hepatic Function

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.

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.

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.

Clostridioides difficile-Associated Diarrhea

Drugs that elevate intragastric pH may be associated with an increased risk of Clostridium difficile gastrointestinal infection. Pseudomembranous colitis may be due to antibiotics used such as amoxicillin hydrate or clarithromycin for Helicobacter pylori eradication in combination with vonoprazan. If abdominal pain and frequent diarrhea occur, appropriate measures, including discontinuation of the treatment, should be taken.

Bone Fracture

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 with the use of proton pump inhibitors, especially with use of high doses over a long-term period (>1 year). The mechanism is not clear and is likely to be multifactorial.

Hypomagnesemia and Mineral Metabolism

Hypomagnesemia has been reported postmarketing with vonoprazan. Hypomagnesemia may lead to hypocalcemia and/or hypokalemia and may exacerbate underlying hypocalcemia in at-risk patients.

Consider monitoring magnesium and calcium levels prior to initiation of Vonotec (Vonoprazan) and periodically while on treatment in patients with a preexisting risk of hypocalcemia (e.g., hypoparathyroidism). Supplement with magnesium and/or calcium, as necessary. If hypocalcemia is refractory to treatment, consider discontinuing Vonotec (Vonoprazan).

Fundic Gland Polyps

Use of Vonotec (Vonoprazan) is associated with a risk of fundic gland polyps that increases with long-term use, especially beyond one year. Fundic gland polyps have been reported with vonoprazan in clinical trials and postmarketing use with PPIs. Use the shortest duration of Vonotec (Vonoprazan) appropriate to the condition being treated.

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.

Use in Children

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

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. Vonoprazan should be administered with care when co-administered with the following drugs:

With strong CYP3A4 inhibitors, e.g., clarithromycin or Amoxicillin

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 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.

With low dose of aspirin or NSAID

There were no clinically significant effects of low-dose aspirin or NSAIDs on the pharmacokinetics of vonoprazan, and no clinically significant effects of vonoprazan on the pharmacokinetics of low-dose aspirin or NSAIDs. The effect on platelet-aggregating inhibitory activity of low-dose aspirin was not considered clinically meaningful.

Antiretrovirals

Vonoprazan reduces intragastric acidity which may alter the absorption of antiretroviral drugs leading to changes in the safety and/or effectiveness.

Other Drugs (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole/itraconazole)

Vonoprazan reduces intragastric pH which may decrease the absorption of drugs reducing their effectiveness.

Certain CYP3A Substrates where minimal concentration changes may lead to serious toxicities

Vonoprazan is a weak CYP3A inhibitor. Vonoprazan may increase exposure of CYP3A4 substrates, which may increase the risk of adverse reactions related to these substrates. Frequent monitoring for concentrations and/or adverse reactions related to the substrate drugs when used with Vonotec (Vonoprazan). Dosage reduction of substrate drugs may be needed.

CYP2C19 Substrates (e.g., clopidogrel, citalopram, cilostazol)

Vonoprazan is a CYP2C19 inhibitor. Vonoprazan may reduce plasma concentrations of the active metabolite of clopidogrel and may cause reduction in platelet inhibition. Vonoprazan may increase exposure of CYP2C19 substrate drugs (e.g., citalopram, cilostazol). Carefully monitor the efficacy of clopidogrel and consider alternative anti-platelet therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

During treatment with Vonoprazan, nursing should be avoided if the administration of this drug is necessary for the mother.

Fertility

No studies on the effect on human fertility have been conducted for Vonoprazan. Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

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

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, y-GPT increased, edema and eosinophilia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested 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: Proton Pump Inhibitors.

ATC code: A02BC08

Mechanism of action

Vonoprazan suppresses basal and stimulated gastric acid secretion at the secretory surface of the gastric parietal cell through inhibition of the H+, K+-ATPase enzyme system in a potassium competitive manner. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, vonoprazan has been characterized as a type of gastric proton-pump inhibitor, in that it blocks the final step of 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.

Pharmacodynamics

Antisecretory Activity

Following a single 10 mg or 20 mg dose of vonoprazan, the onset of the antisecretory effect as measured by intragastric pH occurs within 2 to 3 hours. 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.

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

Absorption

Vonoprazan exhibits time independent pharmacokinetics and steady state concentrations are achieved by Day 3 to 4. After multiple doses of vonoprazan ranging from 10 to 40 mg (twice the maximum recommended dose) once daily for 7 days in healthy subjects, Cmax and area under the plasma concentration time curve (AUC) values for vonoprazan increased in an approximately dose proportional manner. There is little accumulation in plasma after once daily multiple doses, with an accumulation index ratio of less than 1.2 based on AUC for doses ranging from 10 to 40 mg (twice the maximum recommended dose).

Absolute bioavailability has not been determined. The pharmacokinetic parameters of vonoprazan following single administration of vonoprazan to healthy adult male subjects at 20 mg under fasting and fed conditions are as follows:

Under fasting: Tmax 1.5 h (1.0-3.0), Cmax 24.3 ± 6.6 ng/mL, T1/2 7.7 ± 1.0 h, AUC48 222.1 ± 69.7 h.ng/mL.

After meal: Tmax 3.0 h (1.0-4.0), Cmax 26.8 ± 9.6 ng/mL, T1/2 7.7 ± 1.2 h, AUC48 238.3 ± 71.1 h.ng/mL.

(Mean ± S.D. of 12 subjects; tmax is expressed as the median (minimum value, maximum value)).

Distribution

Plasma protein binding of vonoprazan ranged from 85 to 88% in healthy subjects and was independent of concentration from 0.1 to 10 mcg/mL.

Metabolism

Vonoprazan is metabolized to inactive metabolites via multiple pathways by a combination of cytochrome P450 (CYP) isoforms (CYP3A4/5, CYP2B6,

CYP2C19, CYP2C9 and CYP2D6) along with sulfo- and glucuronosyl-transferases.

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).

Elimination

Following oral administration of radiolabeled vonoprazan, approximately 67% of the radiolabeled dose (8% as unchanged vonoprazan) was recovered in urine and 31% (1.4% as unchanged vonoprazan) was recovered in feces.

Specific Populations

Patients with Renal impairment

The pharmacokinetics of vonoprazan administered as a single 20 mg dose in patients with mild, moderate, or severe renal impairment were compared to those with normal renal function. Compared to subjects with normal renal function, systemic exposure (AUC0-inf) was 1.7-, 1.3-, and 2.4-times greater in patients with mild, moderate, and severe renal impairment, respectively. In subjects requiring dialysis, AUC0-inf estimates were 1.3-fold greater compared to estimates from subjects with normal renal function. Protein binding of vonoprazan is not affected by impaired renal function. In patients requiring dialysis, vonoprazan was present in the dialysate and represented 0.94% of the dose administered.

Patients with Hepatic impairment

The pharmacokinetics of vonoprazan administered as a single 20 mg dose in patients with mild, moderate or severe hepatic impairment were compared to those with normal hepatic function. Compared to subjects with normal hepatic function, systemic exposure (AUC0-inf) of vonoprazan was 1.2-, 2.4-, and 2.6-times greater in patients with mild, moderate, and severe hepatic impairment, respectively. Protein binding of vonoprazan is not affected by impaired hepatic function.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- D-Mannitol
- Microcrystalline Cellulose (Avicel pH 102)

- Croscarmellose Sodium
- Low-substituted hydroxypropyl cellulose (L-HPC)-11
- Fumaric Acid
- Magnesium Stearate
- Hydroxypropyl Methylcellulose (Pharmacoat 606)
- Titanium Dioxide
- Polyethylene glycol 6000 (PEG)
- Iron Oxide Red

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years (24 months)

6.4 Special precautions for storage

Store below 30°C.

Protect from heat, light and moisture.

To be sold on the prescription of a registered Medical practitioner only.

6.5 Nature and contents of container

Vonotec (Vonoprazan) 20mg Tablet available in Alu-Alu blister pack of 28's (4 X 7's) tablets packed in a unit printed carton along with package insert.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Name: Pharmatec Pakistan (Pvt.) Ltd.

Address: D-86/A, S.I.T.E., Karachi-75700, Pakistan.

Telephone No.: 021-32561155-8

Fax No.: 32561330

Website: www.pharmatec.com

Email: info@pharmatec.com, hilal.ahmed@pharmatec.com

8. MARKETING AUTHORISATION NUMBER(S)

H2026/CTD12204/26806

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

May 15th, 2024

10. DATE OF REVISION OF THE TEXT

22-08-2026