Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Tumivono 10 mg, 20mg

2. Qualitative and quantitative composition:
Each film coated

Each film coated tablet contains:

vonoprazan..... 10 mg.

Each film coated tablet contains:

vonoprazan..... 20 mg.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form
Film-coated tablet.

A light yellow coloured, round shaped, biconvex, film coated tablet, break line on one side plain on other side.

4. Clinical particulars

4.1 Therapeutic indications
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.

4.2 Posology and method of administration
Posology
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 Vono-Q(Vonoprazan) administered orally once daily

Adjunct to Helicobacter pylori eradication:

Usually, the following 3 drugs are orally administered at the same time twice daily for 7 days: 10 mg vonoprazan, 750 mg amoxicillin, and 200 mg clarithromycin. The dose of clarithromycin may be appropriately increased as required, however, the upper limit is 400 mg twice daily. When Helicobacter pylori eradication treatment with 3 drugs consisting of a proton pump inhibitor, amoxicillin, and clarithromycin fails, alternative treatment with the following 3 drugs is recommended; 10 mg vonoprazan, 750 mg amoxicillin, and 250 mg 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

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

Hepatotoxicity:

Hepatic function abnormalities including liver injury have been reported in clinical studies (see Adverse Reactions). 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 associated diarrhea, including pseudomembranous colitis: 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 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.

Renal Impairment: 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. (See Pharmacology: Pharmacokinetics under Actions.)

Hepatic Impairment:

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. (See Pharmacology: Pharmacokinetics under Actions.)

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. (See Renal Impairment and Hepatic Impairment as previously mentioned).

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 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 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 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 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.

Not applicable

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 (CCT-003 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 non-erosive 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 active-comparator 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 analysed separately. (Note: AG-1749 (Lansoprazole) is the only comparator used in the comparator studies.) (See Table 4.)

Post marketing:

Following is a list of ADRs which have been observed in post marketing and are not included in the table previously:

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 category: - vonoprazan ; Belongs to the class of potassium-competitive acid blocker. Used in the treatment of peptic ulcer and gastro-oesophageal reflux disease (GERD). Proton Pump Inhibitor.

Pharmacology:

Mechanism of Action:

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.

Serum Gastrin and Serum Pepsinogen Effects:

Increased serum gastrin and serum pepsinogen concentrations are physiological responses to treatment with acid suppression therapy, including vonoprazan. Increased serum gastrin and serum pepsinogen concentrations were reported with a higher incidence in the vonoprazan treatment groups compared with lansoprazole treatment groups. Serum gastrin and serum pepsinogen concentrations returned to baseline over time upon discontinuation of vonoprazan. The increase in serum gastrin concentration occurred early in treatment with vonoprazan and remained stable for the remainder of treatment.

Clinical Studies:

The efficacy of vonoprazan has been demonstrated in a number of clinical studies across several indications including GU, DU, RE, prevention of GU/DU during NSAID administration and as an adjunct to H. pylori eradication. Clinical efficacy in completed phase 2 and 3 studies is summarized in Table 1. These data are divided into the categories based upon the specific indication, including GU, DU, RE, prevention of recurrence of gastric or duodenal ulcer during NSAID administration, and H. pylori eradication.

Following administration of vonoprazan at a dose of 10 mg or 20 mg in healthy adult male subjects for 7 days, pH 4 HTR (pH 4 holding time ratio) (percentage of time pH is maintained at a level ≥ 4 in 24 hours) was 63±9% and 83±17% respectively. A phase 1 open-label pharmacodynamics study to investigate the acid-inhibitory effect of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole sodium 10 mg in healthy adult male Japanese subjects showed that the acid-inhibitory effect of vonoprazan was greater than that of esomeprazole or rabeprazole. After all treatments, the mean 24-hour pH 4 HTRs increased from Baseline to Day 1 and from Day 1 to Day 7. The mean pH 4 HTRs were higher after administration of vonoprazan on Day 1 than after administration of esomeprazole or rabeprazole on Day 7. The mean 24-hour pH 4 HTRs for vonoprazan and rabeprazole at Baseline were both 8.9%, and on Day 1 and on Day 7 were 84.16% vs 26.29%, and 93.79% vs 65.09%,

5.2 Pharmacokinetic properties

Pharmacokinetics at single administration: Following 7 day repeat once daily doses of vonoprazan at doses of 10-40 mg, in healthy adult male subjects, $AUC_{\tau,ss}$ and $C_{max,ss}$ increase in a slightly greater than dose proportional manner. 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, vonoprazan does not exhibit time-dependent pharmacokinetics. The following table shows pharmacokinetic parameters of vonoprazan on day 7 of administration. Mean±S.D. of 9 subjects (tmax is expressed by the median (minimum value, maximum value)). Absorption: 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 presented in the table as follows: Mean±D.S. of 12 subjects (tmax is expressed by the median (minimum value, maximum value). Distribution: The mean binding rate is 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 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 and Elimination:

When radioactive-labelled drug (15 mg as vonoprazan) is orally administered to healthy adult male subjects, 98.5% of the radioactivity administered is excreted into urine and faeces by 168 hours after administration: 67.4% into urine and 31.1% into faeces

Special Populations:

Impaired Renal Function: The effect of renal disorders on pharmacokinetics of vonoprazan was evaluated in subjects with normal renal function and patients with mild, moderate or severe renal disorder and patients with end-stage renal disease (ESRD). When administered a single dose of vonoprazan 20 mg, the AUC∞ was higher by 1.3 to 2.4 times and the Cmax higher by 1.2 to 1.8 times, in patients with mild, moderate or severe renal disorder compared to subjects with normal renal function indicating an increase in vonoprazan exposure with a reduction in renal function. The AUC∞ was higher by 1.3 times and the Cmax higher by 1.2 times in ESRD patients compared to those in subjects with normal renal function.

Impaired Hepatic Function:

The effect of hepatic disorders on pharmacokinetics of vonoprazan was evaluated in subjects with normal hepatic function and patients with mild, moderate or severe hepatic disorder. When administered a single dose of vonoprazan 20 mg, the AUC∞ was higher by 1.2 to 2.6 times and Cmax higher by 1.2 to 1.8 times in patients with mild, moderate or severe hepatic disorder compared to subjects with normal hepatic function. Age, Gender, Race: Vonoprazan has not been studied in patients under 18 years of age. There are no clinically relevant gender effects of vonoprazan. No dedicated ethnic comparison studies have been conducted with vonoprazan. The ethnic sensitivity analysis based on the International Conference for Harmonization (ICH) E5 principles was conducted to assess whether the molecular properties of vonoprazan were sensitive to ethnic factor differences, and whether the diagnosis, medical practice, treatment options and other epidemiological factors for acid-related disorders would vary dramatically in areas other than Japan. It was concluded that vonoprazan is insensitive to ethnic factor differences.

Drug Interactions:

Vonoprazan and clarithromycin: Healthy adult male subjects were administered with a single dose of vonoprazan (40 mg), 30 minutes after breakfast on day 1 and day 8, and with repeated dose of clarithromycin 500 mg (potency) 2 times daily 30 minutes before breakfast and dinner on day 3 - 9. The AUC∞ and Cmax of vonoprazan increased by 1.6 times and 1.4 times, respectively, when concomitantly administered with clarithromycin compared to those of vonoprazan when administered alone.

Vonoprazan, amoxicillin and clarithromycin:
The drug interaction study in healthy adult male subjects administered twice daily with vonoprazan 20 mg, amoxicillin 750 mg (potency) and clarithromycin 400 mg (potency) concomitantly for 7 days shows no effect on pharmacokinetics of unchanged amoxicillin, however, AUC12 and Cmax of vonoprazan increased by 1.8 times and 1.9 times, respectively, and AUC12 and Cmax of unchanged clarithromycin increased by 1.5 times and 1.6 times, respectively.

Vonoprazan, amoxicillin and metronidazole:
The drug interaction study in healthy adult male subjects administered twice daily with vonoprazan 20 mg, amoxicillin 750 mg (potency) and metronidazole 250 mg concomitantly for 7 days showed little difference in the pharmacokinetics of vonoprazan, when administered alone or as triple therapy. No difference was observed in the pharmacokinetics of metronidazole or amoxicillin when administered alone or as triple therapy.

Vonoprazan and NSAIDs:
The drug interaction study in healthy adult male subjects administered with vonoprazan 40 mg and NSAID (loxoprofen sodium 60 mg, diclofenac sodium 25 mg or meloxicam 10 mg) concomitantly showed no clear effect of NSAIDs on pharmacokinetics of vonoprazan and of vonoprazan on pharmacokinetics of NSAIDs.

Vonoprazan and Midazolam:
The drug interaction study in 20 healthy adult male and female subjects administered single oral doses of 2 mg of midazolam syrup on Days 1 and 9 and oral doses of vonoprazan 20 mg twice-daily on Days 2 through 10 showed that steady-state plasma midazolam Cmax and AUC∞ values were 93% and 89% higher, respectively, than when midazolam was administered alone. Likewise, steady-state plasma 1-hydroxymidazolam (main and active midazolam metabolite mediated by CYP3A4) Cmax and AUC values were 25-37% higher than when midazolam was administered alone. Since midazolam systemic exposure increased less than 2-fold when co-administered with oral vonoprazan, vonoprazan is classified as a weak inhibitor of CYP3A4.

Toxicology:
Nonclinical 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. The NOAEL was < 6 mg/kg/day.
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 prior to 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.

5.3 Preclinical safety data
Not applicable

6. Pharmaceutical particulars
List of excipients

Microcrystalline Cellulose (PH 101), Mannitol Croscarmellose sodium ,L-HPC 21 PEG-6000, Purified Water, Magnesium Stearate, DRCOAT FCU Isopropyl alcohol, Methylene Dichloride

6.1 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.2 Shelf life

36 months

6.3 Special precautions for storage:

Store below 30°C. Protect from moisture.

6.4 Nature and contents of container

10 tablets in Alu-Alu blister pack, 3 such blisters in a printed carton along with Pack Insert

6.5 Special precautions for disposal and other handling:

The medicinal product must be used immediately after opening any remaining solution must be discarded.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:
Company) Name: OMILIFE LIMITED
Address: P.O. BOX 524-00200 CITY SQUARE, NAIROBI, KENYA.
Telephone: +254 723353615
E-Mail:omilifebio@gmail.com
Manufacturing site address:
4Care Life Science(P) limited
Address: survey No.23/3P&24, Opp. Jeans Factory, Daduram Vistar, Village –Bagdol, Tal-kathlal, Dist-Kheda-387630, Gujarat, India
Country: India
E-Mail: tushar@4care.in

8. Marketing authorization number

CTD10509

9. Date of first registration

03/08/2023

10. Date of revision of the text:

September 2023

11. Dosimetry:

Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:

Not Applicable

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