CABVON (Vonoprazan) Tablets 10mg, 20mg

کیب وان ٹیبلٹس ۱۰ ملی گرام ۲۰ ملی گرام (ووناپرازان)

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Vonoprazan fumarate eq. to Vonoprazan.....10mg
(Innovator's Specifications)
Vonoprazan fumarate eq. to Vonoprazan.....20mg
(Innovator's Specifications)

DESCRIPTION: Vonoprazan is a potassium competitive acid blocker (PCAB) and inhibits H+, K+-ATPase in a reversible and potassium-competitive manner used for the treatment of gastric ulcer, duodenal ulcer, or reflux esopha-gitis.

CLINICAL 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. **Pharmacodynamics:** Serum Gastrin and Serum Pepsinogen Effects: Increased serum gastrin and serum pepsinogen concentrations are physiological responses to treatment with acid suppression therapy, including vonoprazan. In-creased 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 ad-ministration 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%, respectively. **Pharmacokinetics: Pharmacokinetics at single administration:** Following 7 day repeat once daily doses of vonoprazan at doses of 10-40 mg, in healthy adult male subjects, AUCτ,ss and Cmax,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 condi-tions are presented in the table as follows:

Table 3.

Dose	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
T 1/2 (h)	7.7±1.0	7.7±1.2
AUC 48 (h-ng/mL)	222.1±69.7	238.3±71.1

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 addi-tion, 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-labeled drug (15 mg 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. Specific Populations. **Patients with Renal Impairment:** 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. **Patients with Hepatic Impairment:** 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. **Effects of Age, Body Weight, Gender, and 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 proper-ties 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 Interaction Studies . **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 clarithromy-cin 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 hydrate and clarithromycin:** The drug interaction study in healthy adult male sub-jects administered twice daily with vonoprazan 20 mg, amoxicillin hydrate 750 mg (potency) and claritho-mycin 400 mg (potency) concomitantly for 7 days shows no effect on pharmacokinetics of unchanged amox-icillin, 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 hydrate and metronidazole:** The drug interaction study in healthy adult male sub-jects administered twice daily with vonoprazan 20 mg, amoxicillin hydrate 750 mg (potency) and metroni-dazole 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 met-ronidazole or amoxicillin when administered alone or as triple therapy. **Vonoprazan and NSAIDs:** The drug interaction study in healthy adult male subjects administered with vonoprazan 40mg and NSAID (loxoprofen sodium 60mg, 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.

INDICATIONS

- 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) 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 thrombocytopenic purpura, the stomach after endoscopic resection of early stage cancer, or Helicobacter pylori gastritis.

CONTRAINDICATIONS: Hypersensitivity to the active ingredients or to any of the excipients.

INTERACTIONS: 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 con-centrations of vonoprazan by up to 1.9-fold. No increase was observed with the antibiotic regimen of met-ronidazole 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 clini-cally significant effects of vonoprazan on the pharmacokinetics of NSAIDs.

USE IN SPECIFIC POPULATION: 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 thera-peutic 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 vonopra-zan was excreted in milk. During treatment with vonoprazan, nursing should be avoided if the administra-tion of this drug is necessary for the mother. **Paediatric Use:** Vonoprazan has not been studied in patients under 18 years of age. **Geriatric Use:** Since the physiological functions such as hepatic or renal function are decreased in elderly patients in gen-eral, vonoprazan should be carefully administered. **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. **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. **ADVERSE REACTIONS:** 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). Alt-hough 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 num-ber 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 analyzed separately. (Note: AG-1749 (Lanso-prazole) is the only comparator used in the comparator studies.) (See Table 4.)

Table 4. Adverse reactions with vonoprazan in clinical studies.

Frequency/System Organ Class*	Very Common	Common	Uncommon	Rare
Gastrointestinal disorders		Diarrhoea Constipation	Nausea Abdominal distension	
Investigations			Gamma-glutamyl transferase increased AST increased Liver function test abnormal ALT increased	

* ADRs included as preferred terms arebased on MedDRA version 21.0.

Postmarketing: Following is a list of ADRs which have been observed in postmarketing and are not included in the table previously: (See Table 5.)

Table 5. Adverse reactions with vonoprazan in post marketing setting (Frequency unknown).

System Organ Class	Preferred Term
Immune system disorders	- Drug hypersensitivity (including anaphylactic shock) - Drug eruption - Urticaria
Hepatobiliary disorders	- Hepatotoxicity - Jaundice
Skin and Subcutaneous tissue disorders	- Rash - Erythema multiforme - Stevens-Johnson syndrome Toxic epidermal necrolysis

DOSAGE AND 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 8 weeks. In addition, for the maintenance of healing of reflux esophagitis in patients with repeat recur-rence 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. **Prevention of recurrence of gastric ulcer or duodenal ulcer during NSAIDs administration:** The usual dose is 10 mg of vonoprazan once a day. **Adjunct to Helicobacter pylori eradication:** Usually, the following 3 drugs are orally administered at the same time twice daily for 7 days: 20 mg vonoprazan, 750mg amoxicillin hydrate, and 200mg 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 hydrate, and clarithromycin fails, alternative treatment with the following 3 drugs is recommended; 20mg vonoprazan, 750mg amoxicillin hydrate, 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.

SPECIAL PRECAUTIONS

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 vonopra-zan, many of which occurred shortly after initiation of treatment. Discontinuation of vonoprazan is recom-mended 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 symp-toms 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 intra-gastric pH may be associated with an increased risk of Clostridium difficile gastrointestinal infection. Pseu-domembranous 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 discontin-uation 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.

INSTRUCTIONS

Store below 30°C. Protect from heat, light and moisture. Keep all medicines out of the reach of children. To be sold on the prescription of a registered medical practitioner only.

PRESENTATION

CABVON (Vonoprazan) 10mg Tablets are available in three Alu-Alu blisters of ten tablets (3 x 10's) in a carton with leaf insert.
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ہدایات: خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
۳۰ ڈگری سینٹی گریڈ سے کم پر رکھیں۔ گرمی، روشنی اور نمی سے محفوظ رکھیں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخہ پر فروخت کریں۔
تفصیلی معلومات کے لئے ڈبے میں موجود پرچہ ملاحظہ کیجئے۔

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