

VONO[®] Tablets 10mg (Voprazan) 20mg

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Voprazan fumarate eq. to Voprazan.....10mg

Voprazan fumarate eq. to Voprazan.....20mg

DESCRIPTION: Voprazan 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 esophagitis.

CLINICAL PHARMACOLOGY: Mechanism of Action: Voprazan 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. Voprazan 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 voprazan. In-cresced serum gastrin and serum pepsinogen concentrations were reported with a higher incidence in the voprazan treatment groups compared with lansoprazole treatment groups. Serum gastrin and serum pepsinogen concentrations returned to baseline over time upon discontinuation of voprazan. The increase in serum gastrin concentration occurred early in treatment with voprazan and remained stable for the remainder of treatment. **Clinical Studies:** The efficacy of voprazan 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 voprazan 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 \geq 4 in 24 hours) was 63 \pm 9% and 83 \pm 17% respectively. A phase 1 open label pharmacodynamics study to investigate the acid-inhibitory effect of voprazan 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 voprazan 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 voprazan on Day 1 than after administration of esomeprazole or rabeprazole on Day 7. The mean 24-hour pH 4 HTRs for voprazan 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 voprazan at doses of 10-40 mg, in healthy adult male subjects, AUC₀₋₂₄ and C_{max} increased 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 voprazan is constant between day 3 and day 7 of administration. In addition, voprazan does not exhibit time-dependent pharmacokinetics. The following table shows pharmacokinetic parameters of voprazan on day 7 of administration. Mean \pm S.D. of 9 subjects (t_{max} is expressed by the median (minimum value, maximum value)). **Absorption:** Absolute bioavailability has not been determined. The pharmacokinetic parameters of voprazan following single administration of voprazan to healthy adult male subjects at 20 mg under fasting and fed conditions are presented in the table as follows:

Table 3.	Dose	Under Fasting	After Meal
	t _{max} (h)	1.5 (1.0, 3.0)	3.0 (1.0, 4.0)
	C _{max} (ng/mL)	24.3 \pm 6.6	26.8 \pm 9.6
	AUC (h \cdot ng/mL)	7.2 \pm 1.0	7.7 \pm 1.2
	AUC 4h (h \cdot ng/mL)	222.1 \pm 69.7	238.3 \pm 71.1

Mean \pm S.D. of 12 subjects (t_{max} is expressed by the median (minimum value, maximum value)). **Distribution:** The mean binding rate is 65.2 to 68.0% when [14C] voprazan in the range of 0.1 to 10 μ g/mL is added to human plasma (in vitro). **Metabolism:** Voprazan is metabolized mainly by hepatic drug-metabolizing enzyme CYP3A4 and partially by CYP2B6, CYP2C19 and CYP2D6. Voprazan is also metabolized by sulfotransferase SULT2A1 (in vitro). Voprazan exhibits time-dependent inhibitory effect on CYP2B6, CYP2C19 and

CYP3A4/5 (in vitro). In addition, voprazan 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 voprazan) 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 voprazan 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 voprazan 20 mg, the AUC₀₋₂₄ was higher by 1.3 to 2.4 times and the C_{max} 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 voprazan exposure with a reduction in renal function. The AUC₀₋₂₄ was higher by 1.3 times and the C_{max} 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 voprazan was evaluated in subjects with normal hepatic function and patients with mild, moderate or severe hepatic disorder. When administered a single dose of voprazan 20 mg, the AUC₀₋₂₄ was higher by 1.2 to 2.6 times and C_{max} 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:** Voprazan has not been studied in patients under 18 years of age. There are no clinically relevant gender effects of voprazan. No dedicated ethnic comparison studies have been conducted with voprazan. The ethnic sensitivity analysis based on the International Conference for Harmonization (ICH) E5 principles was conducted to assess whether the molecular properties of voprazan 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 voprazan is insensitive to ethnic factor differences. Drug Interaction Studies. **Voprazan and claritromycin:** Healthy adult male subjects were administered with a single dose of voprazan (40 mg), 30 minutes after breakfast on day 1 and day 8, and with repeated dose of claritromycin 500 mg (potency) 2 times daily 30 minutes before breakfast and dinner on day 3 - 9. The AUC₀₋₂₄ and C_{max} of voprazan increased by 1.6 times and 1.4 times, respectively, when concomitantly administered with claritromycin compared to those of voprazan when administered alone. **Voprazan, amoxicillin hydrate and claritromycin:** The drug interaction study in healthy adult male subjects administered twice daily with voprazan 20 mg, amoxicillin hydrate 750 mg (potency) and claritromycin 400 mg (potency) concomitantly for 7 days shows no effect on pharmacokinetics of unchanged amoxicillin; however, AUC₁₂ and C_{max} of voprazan increased by 1.8 times and 1.9 times, respectively, and AUC₁₂ and C_{max} of unchanged claritromycin increased by 1.5 times and 1.6 times, respectively. **Voprazan, amoxicillin hydrate and metronidazole:** The drug interaction study in healthy adult male subjects administered twice daily with voprazan 20 mg, amoxicillin hydrate 750 mg (potency) and metronidazole 250 mg concomitantly for 7 days showed little difference in the pharmacokinetics of voprazan, 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. **Voprazan and NSAIDs:** The drug interaction study in healthy adult male subjects administered with voprazan 40mg and NSAID (ibuprofen sodium 60mg, diclofenac sodium 25 mg or meloxicam 10 mg) concomitantly showed no clear effect of NSAIDs on pharmacokinetics of voprazan and/or voprazan 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 voprazan 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 voprazan 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. Voprazan is metabolized mainly by hepatic drug-metabolizing enzyme CYP3A4 and partially by CYP2B6, CYP2C19 and CYP2D6. With strong CYP3A4 inhibitors, e.g., claritromycin, blood concentration of voprazan may increase. It has been reported that blood concentration of voprazan increased in concomitant use with claritromycin by 1.5-fold, but no dose adjustment of voprazan is considered necessary. Coadministration of voprazan with the antibiotic regimen claritromycin and amoxicillin increased concentrations of voprazan by up to 1.9-fold. No increase was observed with the antibiotic regimen of metronidazole and amoxicillin. No dose adjustment of voprazan is considered necessary. There were no clinically significant effects of NSAIDs on the pharmacokinetics of voprazan, and no clinically significant effects of voprazan on the pharmacokinetics of NSAIDs.

USE IN SPECIFIC POPULATION: Pregnancy: No clinical studies have been conducted to date to evaluate voprazan in subjects who are pregnant. In a rat toxicology study, embryo-fetal toxicity was observed following exposure of more than approximately 28 times the exposure (AUC) at the maximum clinical dose (40 mg/day) of voprazan. As a precaution, voprazan 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 voprazan in subjects who are lactating. It is unknown whether voprazan is excreted in human milk. In animal studies it has been shown that voprazan was excreted in milk. During treatment with voprazan, nursing should be avoided if the administration of this drug is necessary for the mother.

Paediatric Use: Voprazan 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 general, voprazan should be carefully administered. **Renal Impairment:** Voprazan should be administered with care in patients with renal disorders as a delay in the excretion of voprazan may occur, which may result in an increase in the concentration of voprazan in the blood. **Hepatic Impairment:** Voprazan should be administered with care in patients with hepatic disorders as a delay in the metabolism and excretion of voprazan may occur, which may result in an increase in the concentration of voprazan 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 (\geq 1/10; common (\geq 1/100 < 1/10); uncommon (\geq 1/1,000 < 1/100); rare (\geq 1/10,000 < 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 CCT-001); DU healing (CCT-101); DU healing (CCT-102); prevention of recurrence of peptic ulcer associated with NSAID use (CCT-301, CCT-301 and CCT-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 analyzed separately. (Note: AG-1749 [Lansoprazole] is the only comparator used in the comparator studies.) (See Table 4.)

Table 4. Adverse reactions with voprazan 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 (based 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 voprazan 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 voprazan once a day. Administration should be limited to 8 weeks. **Duodenal ulcer:** The usual dose is 20 mg of voprazan once a day. Administration should be limited to 6 weeks. **Reflux esophagitis (erosive esophagitis):** The usual dose is 20 mg of voprazan 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-rece 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 voprazan 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 voprazan, 750mg amoxicillin hydrate, and 200mg claritromycin. The dose of claritromycin 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 claritromycin fails, alternative treatment with the following 3 drugs is recommended: 20mg voprazan, 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:** Voprazan 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 voprazan, many of which occurred shortly after initiation of treatment. Discontinuation of voprazan 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 voprazan 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 voprazan does not exclude the presence of gastric malignancy. **Clindamycin difficile associated diarrhea, including pseudomembranous colitis:** Drugs that elevate intra-gastric pH may be associated with an increased risk of Clindamycin difficile gastrointestinal infection. Pseudo-membranous colitis may be due to antibiotics used for Helicobacter pylori eradication in combination with voprazan. If abdominal pain and frequent diarrhoea 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.

INSTRUCTIONS

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

PRESENTATION

Vono (Voprazan) 10mg Tablets are available in three Alu-Alu blisters of ten tablets (3 x 10's) in a carton.
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