NAME OF THE MEDICINAL PRODUCT

Vocinti Film-Coated Tablet 10mg
Vocinti Film-Coated Tablet 20mg

NAME AND STRENGTH OF ACTIVE SUBSTANCES

Each tablet contains 10mg and 20mg of Vonoprazan.
Excipients: D-Mannitol, Crystalline Cellulose, Croscarmellose Sodium, Hydroxypropyl Cellulose, Fumaric Acid, Magnesium Stearate, Hypromellose, Macrogol 6000, Titanium Oxide (contained in all products), Yellow Ferric Oxide (contained Vocinti 10 mg Film-Coated Tablet only), Iron Sesquioxide (contained Vocinti 20 mg Film-Coated Tablet only).

PRODUCT DESCRIPTION

Vocinti is supplied as a film-coated tablet containing 10mg or 20mg of vonoprazan:

- 10mg tablet is pale yellow, oval in shape and are printed with “B217” on the upperside
- 20mg tablet is pale red, oval in shape with scored and is printed with “B218” on the upperside

Pharmacological Properties

Pharmacotherapeutic group: Proton Pump Inhibitor
ATC code: A02BC08

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.

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.

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, $AUC_{T,ss}$ 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.

Dose	10 mg	20 mg
t_{max} (h)	1.5 (0.75, 3.0)	1.5 (0.75, 3.0)
$C_{max,ss}$ (ng/mL)	12.0 ± 1.8	23.3 ± 6.6
$t_{1/2}$(h)	7.0 ± 1.6	6.1 ± 1.2
$AUC_{T,ss}$ (h·ng/mL)	79.5 ± 16.1	151.6 ± 40.3

Mean±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 vonoprazan following single administration of vonoprazan to healthy adult male subjects at 20 mg under fasting and fed conditions are presented in the table below:

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 ± 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 (t_{max} 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-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.

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 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 vonoprazan exposure with a reduction in renal function. The AUC ∞ wash 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.

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 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.

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 C_{max} 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, AUC_{12} and C_{max} of vonoprazan increased by 1.8 times and 1.9 times, respectively, and AUC_{12} and C_{max} 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.

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%, respectively.

Table 1. Overview of Clinical Efficacy of vonoprazan (TAK-438) and Comparators in Completed Phase 2 and 3 Studies

Study Name/Design	Vonoprazan Dose(s)	Comparator	Duration (weeks)	Efficacy Endpoints	Efficacy Findings
RE (EE) (healing)					
CCT-001:	5 mg (n=143),	Lansoprazole	8	4-week EE	Non-inferior to

Study Name/Design	Vonoprazan Dose(s)	Comparator	Duration (weeks)	Efficacy Endpoints	Efficacy Findings
Phase 2 dose-ranging in EE	10 mg (n=133), 20 mg (n=144), 40 mg (n=134)	30 mg (n=132)		healing rate	lansoprazole at all doses 4-week EE healing rates: TAK-438 5 mg 92.3%, 10 mg 92.5%, 20 mg 94.4%, 40 mg 97.0%; lansoprazole 30 mg 93.2%
CCT-002: Phase 3 in EE	20 mg (n=205)	Lansoprazole 30 mg (n=199)	8	8-week EE healing rate	Non-inferior to lansoprazole: 99.0% vs 95.5% (p<0.0001)
CCT-003: Phase 3 in EE (treatment period)	20 mg (n=621)	N/A	8	EE healing rate during the treatment period	EE healing rate 98.9%
TAK-438 303: Phase 3 in EE	20 mg (n=238)	Lansoprazole 30 mg (n=230)	Up to 8	8-week EE healing rate	Non-inferior to lansoprazole 8-week EE healing rates: TAK-438 20 mg 92.4%; lansoprazole 30 mg 91.3%
EE (maintenance)					
CCT-003: Phase 3 maintenance in EE (maintenance period)	10 mg (n=197), 20 mg (n=201)	Lansoprazole 15 mg (n=196)		EE recurrence rate	Non-inferior to lansoprazole at both doses: 10 mg 2.5% vs 12.2% (p<0.0001) 20 mg 1.0% vs 12.2% (p<0.0001)
OCT-001: Phase 3 in EE	10 mg (n=149), 20 mg (n=145)	N/A	52	EE recurrence rate	No significant difference observed between treatment groups Recurrence rate TAK-438 10 mg vs 20 mg: Week 12 3.4% vs 2.8%; Week 24 6.0% vs 4.1%; Week 36 6.7 vs 6.9%; Week 52 9.4% vs 9.0%
Gastric Ulcer					
CCT-101: Phase 3 in GU	20 mg (n=231)	Lansoprazole 30 mg (n=225)	8	8-week ulcer healing rate	Non-inferior to lansoprazole: 93.5% vs 93.8% (p=0.011)
Duodenal Ulcer					
CCT-102: Phase 3 in DU	20 mg (n=178)	Lansoprazole 30 mg (n=180)	6	6-week ulcer healing rate	Non-inferiority to lansoprazole not confirmed in Full Analysis Set (FAS) (p=0.0654) Non-inferiority confirmed in PPS
NSAID ulcer recurrence prevention					
CCT-301: Phase 3 in patients with healed ulcer receiving NSAIDs	10 mg (n=209), 20 mg (n=203)	Lansoprazole 15 mg (n=199)	24	24-week ulcer recurrence rate	Non-inferior to lansoprazole at both doses: 10 mg 3.3% vs 5.5% (p<0.0001) 20 mg 3.4% vs 5.5% (p<0.0001)

Study Name/Design	Vonoprazan Dose(s)	Comparator	Duration (weeks)	Efficacy Endpoints	Efficacy Findings
OCT-301: Phase 3 in patients with healed ulcer receiving NSAIDs (extension)	10 mg (n=209), 20 mg (n=203)	Lansoprazole 15 mg (n=199)	28-80	Ulcer recurrence rate	Ulcer recurrence rates were lower at all visits in the TAK-438 groups than in the lansoprazole group TAK-438 10 mg vs 20 mg vs lansoprazole 15 mg Week 52 3.8% vs 5.4% vs 7.0% Week 76 3.8% vs 5.9% vs 7.5% Week 104 3.8% vs 5.9% vs 7.5%
H pylori eradication					
CCT-401 first-line: Phase 3 in H pylori	20 mg + amoxicillin and clarithromycin (n=324)	Lansoprazole 30 mg + amoxicillin and clarithromycin (n=320)	1	4-week eradication rate	Non-inferior to lansoprazole: 92.6% vs 75.9% (p<0.0001)
CCT-401 second-line: Phase 3 in H. *pylori*	20 mg + amoxicillin *and metronidazole (n=50)*	N/A	1	4-week eradication rate	4-week eradication rate: 98%

N/A=not assessed, PPS=per protocol set, FAS=.Full Analysis Set
EE = Erosive Esophagitis = Reflux Esophagitis (RE).

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.

INDICATION

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. The duration of administration in the long-term efficacy clinical Study OCT-001 is up to 52 weeks.
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

DOSAGE AND ADMINISTRATION

Adults

Gastric ulcer

The recomended dose is 20 mg of vonoprazan once a day. Administration should be limited to 8 weeks.

Duodenal ulcer

The recomended dose is 20 mg of vonoprazan once a day. Administration should be limited to 6 weeks.

Reflux esophagitis (erosive esophagitis)

The recomended 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 recurrence 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. The duration of administration in the long-term efficacy clinical Study OCT-001 is up to 52 weeks.

Prevention of recurrence of gastric ulcer or duodenal ulcer during NSAIDs administration

The recomended dose is 10 mg of vonoprazan once a day.

Adjunct to Helicobacter pylori eradication

Vonoprazan should be administered in accordance with one of the regimens listed below to eradicate *H pylori* infections. Healthcare professionals should refer to local guidance for antibiotic use to determine the most appropriate regimen and duration of treatment.

It is recommended that the following 3 drugs are orally administered at the same time twice daily for 7 days: 20 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; 20 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.

CONTRAINDICATION

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

WARNINGS AND PRECAUTIONS

Hepatotoxicity

Hepatic function abnormalities including liver injury have been reported in clinical studies (see Section Adverse Event). 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.

Interference with Laboratory Tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumors. To avoid this interference, vonoprazan treatment should be stopped 14 days before CgA measurements.

INTERACTION WITH OTHER MEDICATIONS AND OTHER FORMS OF 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 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.

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.

Model-Informed Effect of CYP3A Inducers on Vonoprazan: Vonoprazan is a CYP3A substrate. The effects of a strong or moderate CYP3A4 inducer on the exposure of orally administered vonoprazan were evaluated using simulations with a Physiologically Based Pharmacokinetic (PBPK) model. Vonoprazan exposures are predicted to be 80% lower when co-administered with a strong CYP3A4 inducer such as rifampicin and 50% lower when co-administered with a moderate CYP3A4 inducer such as efavirenz. Avoid concomitant use of strong or moderate CYP3A inducers with vonoprazan.

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.

USE IN SPECIFIC POPULATIONS

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 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.

Pediatric 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 general, vonoprazan should be carefully administered. (See Renal Impairment and Hepatic Impairment sections below).

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 Section Pharmacokinetics).

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 Section Pharmacokinetics).

ADVERSE 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 analyzed separately. (Note: AG-1749 (Lansoprazole) is the only comparator used in the comparator studies.)

Table 2. 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	

Postmarketing
Following is a list of ADRs which have been observed in postmarketing and are not included above:

Table 3. 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

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.

STORAGE CONDITIONS
Store below 30°C.

Shelf life
3 years

PACKAGING AVAILABLE
Pack of 10 Tablets (Sample) or 30 Tablets.

NAME AND ADDRESS OF MANUFACTURER/MARKETING AUTHORIZATION HOLDER
Manufacturer
Takeda Pharmaceutical Company Limited
(Hikari Plant)
4720 Takeda, Mitsui, Hikari, Yamaguchi
743-8502, Japan

Product Registration Holder
Takeda Malaysia Sdn Bhd
Unit TB-L13-1, Level 13, Tower B, Plaza 33
No. 1, Jalan Kemajuan, Seksyen 13
46200 Petaling Jaya, Selangor, Malaysia

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