Taiwan Food and Drug Administration

Assessment Report

Trade Name：福星定膜衣錠 20 毫克/
Vocinti Film-Coated Tablets 20mg

Active Ingredient：Vonoprazan Fumarate (TAK-438)

License Number：MOHW-PI 027623

Applicant：台灣武田藥品工業股份有限公司

Approval Date：2019/08/12

Indication：糜爛性食道炎(EE)的治療及維持治療。
Treatment and maintenance treatment of erosive esophagitis.

1. **Background Information**

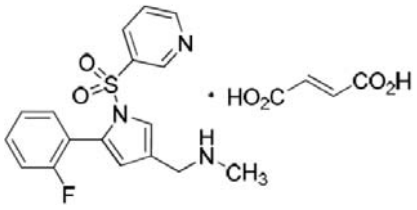
Trade Name	福星定膜衣錠 20 毫克/Vocinti Film-Coated Tablets 20mg
Active Ingredient(s)	Vonoprazan Fumarate (TAK-438)
Applicant	台灣武田藥品工業股份有限公司
Dosage Form & Strengths	膜衣錠 20
Indication	糜爛性食道炎(EE)的治療及維持治療。 Treatment and maintenance treatment of erosive esophagitis.
Posology	For the treatment of erosive esophagitis, the adult dose for oral use is 20 mg of vonoprazan administered once daily up to 8 weeks. For the maintenance therapy of erosive esophagitis, the dose for oral use is 10 mg once daily for 6 months. Vonoprazan can be taken without regard to food or timing of food.
Pharmacological Category **ATC Code**	None

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug Substance

The drug substance, vonoprazan fumarate, is chemically designated as 1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-*N*- methylmethanamine monofumarate and has the following structure:



It is white powder. The molecular formula and the molecular weight are $C_{17}H_{16}FN_3O_2S•C_4H_4O_4$ and 461.46, respectively. It is non-hygroscopic and slightly soluble in water.

Adequate information of characterization of the drug substance has been provided. The molecular structure of vonoprazan fumarate has been confirmed by elemental analysis, UV, IR, NMR, MS and single crystal x-ray crystallography.

The specification includes tests for appearance, crystal form, identification, heavy metals, related substances, residual solvents, water content, residue on ignition, particle size and assay.

2.1.2 Drug Product

Vocinti® Film-Coated Tablets are rapid-release tablets, oval film coated tablets produced in 10 mg and 20 mg of vonoprazan (equivalent to 13.36 mg and 26.72 mg of vonoprazan fumarate, respectively), which are distinguished by size, by color, and by dose specific imprinted markings on one side. The excipients used in the drug product formulation comply with the compendial monographs.

The drug product release specifications include appearance, identification, related substances, content uniformity, dissolution and assay. Analytical methods are described well and validated.

Stability studies of Vocinti® Film-Coated Tablets under long term condition (30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Vonoprazan belongs to a new class of acid-inhibitory agents called “potassium-competitive acid blockers” (P-CAB). P-CABs directly and ionically (i.e., reversibly) bind to (or adjacent to) the K^+-binding region of the catalytic subunit of H^+, K^+-ATPase (proton pump), competitively preventing the binding of K^+ required for the conformational changes necessary for continued acid secretion, effectively blocking the exchange of K^+ for H^+, thereby halting the secretion of gastric acid.

In vitro pharmacodynamic studies demonstrated that vonoprazan potently and selectively inhibits the gastric H^+, K^+-ATPase. Vonoprazan was approximately 5-fold more potent than another PCAB (SCH-28080), and more than 300-fold more potent than the PPIs lansoprazole or esomeprazole in its inhibition of the gastric proton pump. Vonoprazan was also about 300- to 500-fold more potent than that of the highly homologous Na^+, K^+-ATPase enzyme, demonstrating high selectivity.

In vivo pharmacodynamics studies in rats and dogs showed that vonoprazan dose-dependently and significantly inhibited gastric acid secretion and prevented the formation of aspirin- and indomethacin-induced mucosal lesion. Furthermore, vonoprazan was about twice as potent as lansoprazole as an inhibitor of thoracic esophageal lesion

formation. Secondary pharmacodynamics study had revealed some off-target effects of vonoprazan at μM concentrations, including inhibitions of muscarinic M1, muscarinic M3, L-type calcium channel, and 5-HT_2 receptors.

Safety pharmacology studies indicated that vonoprazan had minimal acute pharmacological effects on the central nervous, cardiovascular, or respiratory systems of rats and dogs. Some autonomic signs (e.g., mydriasis, lacrimation, salivation, decrease in muscle resistance…*etc*.) were observed with high dose of vonoprazan in the CNS study and acute toxicity studies. An IC_{50} value of 4.8 μg/mL was reported for hERG channels, and the safety margin was calculated to be >1400-fold after consideration of the plasma exposure in humans at the highest proposed clinical dose (20 mg dose) and available free drug (based upon human protein binding data).

2.2.2 Toxicological Studies

General toxicology studies of vonoprazan have been conducted up in rats (up to 26 weeks), and dogs (up to 39 weeks). After repeat-dose toxicity testing, target organs were identified as stomach (all species), liver (rat), adrenal gland (rat) and thyroid (rat). The NOAELs of vonoprazan were 5 mg/kg (males) and 10 mg/kg (females) in the 26-week rat study, and 0.6 mg/kg in the 39-week dog study. Based on human exposure at 20 mg dose, safety margins are 1.4~10.7 fold and 2.3~2.7 fold in rats and dogs, respectively.

Vonoprazan was not genotoxic and phototoxic, but it dose-dependently increased the incidence of gastric neuroendocrine cell tumor and liver tumor in mouse and rat. 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 development of neuroendocrine tumor in rodent is considered to be of little relevance to humans, and the hepatic tumors occurred at approximately more than 13 times (mouse) and approximately more than 58 times (rat) of the clinical exposure.

Vonoprazan at high dose had been shown to impair the development of rat's fetus and pup; however, these toxicities are not expected to occur in human patients at the proposed clinical dose. The hepatic findings noted in the rat PPND study were transient, and resolved with further growth of the animals.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The absolute bioavailability of vonoprazan tablet has not been determined. The C_{max} was reached at approximately 1.5 hours after oral administration. After multiple doses given once daily for 7 days, plasma concentrations reached a steady state by Day 3 and no time

dependency accumulation was observed in healthy subjects. Mean C_{max} and $AUC_{0\text{-}tau}$ increased slightly more than dose proportionally across 10 mg to 40 mg after single or multiple doses. The food impact on the absorption of vonoprazan was limited, thus vonoprazan can be taken without regard to food. There would be no essential difference in PK of vonoprazan between the patients with erosive esophagitis and healthy subjects.

The protein binding of vonoprazan ranged from 85% to 88%. *In vitro* studies showed that vonoprazan was metabolized primarily by CYP3A4 and partly by CYP2B6, CYP2C19 and CYP2D6. Several major metabolites (M-I, M-II, M-III, M-IV-Sul, and M-I-G) were formed in body but almost inactive compared to the parent drug. After oral administration of radiolabeled vonoprazan, 67.38% of administered radioactivity was excreted in urine and 31.08% was excreted in feces. The terminal half-life observed in healthy subjects is approximately 7.7 hours.

2.3.2 Interaction Studies

Because gastric antisecretory effect of vonoprazan may reduce solubility or absorption of some co-administered drugs, vonoprazan should not be co-administered with atazanavir sulfate and rilpivirine hydrochloride; vonoprazan should be used with caution when co-administered with itraconazole, tyrosine kinase inhibitors and nelfinavir mesylate. Gastric antisecretory effect of vonoprazan may inhibit hydrolysis of digoxin. It has been reported that blood concentration of vonoprazan increased in concomitant use with clarithromycin. Therefore, vonoprazan should be used with caution when co-administered with digoxin, methyldigoxin and CYP3A4 inhibitors.

2.3.3 Special Populations

Two clinical trials were conducted to evaluate the effect of hepatic and renal impairment, respectively on PK of vonoprazan with a single dose of 20 mg vonoprazan. The $AUC_{0\text{-}inf}$ and C_{max} were higher by 1.2-2.6 times and 1.2-1.8 times, respectively, in patients with mild, moderate, and severe hepatic impairment, compared to subjects with normal hepatic function. The $AUC_{0\text{-}inf}$ and C_{max} were higher by 1.3-2.4 times and 1.2-1.8 times, respectively, in patients with mild, moderate, and severe renal impairment compared to subjects with normal renal function. The $AUC_{0\text{-}inf}$ and C_{max} were higher by 1.3 times and 1.2 times, respectively, in ESRD patients compared to those with normal renal function. Vonoprazan should be used with caution in patients with hepatic or renal impairment.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

A total of three randomized, multicenter, double-blind, active controlled, Phase 3 studies ([TAK-438/CCT-002], [TAK-438_303], and [TAK-438/CCT-003]) were reviewed to

evaluated the efficacy of Vocinti (vonoprazan) for healing erosive esophagitis (EE) and maintaining healing of EE in patients with repeat recurrence and relapse of the condition.

The first two studies ([TAK-438/CCT-002] and [TAK-438_303]) were conducted to assess the efficacy and safety of vonoprazan 20 mg in the treatment of EE. Study [TAK-438/CCT-003] was conducted in patients with EE that had been successfully healed by vonoprazan to evaluate the efficacy of vonoprazan (10 mg and 20 mg) for maintenance treatment of EE.

The primary endpoint for the first two studies is the EE healing rate during the 8-week treatment period. In Study [TAK-438/CCT-003], the primary endpoint is the EE recurrence rate at Week 24 in the maintenance period.

In Study [TAK-438/CCT-002], results of the primary analysis showed that the EE healing rate in vonoprazan 20 mg group (99.0%) was non-inferior to that in the lansoprazole 30 mg group (95.5%) during the 8-week treatment period. In Study [TAK-438_303], results of the primary analysis showed that the EE healing rate in vonoprazan 20 mg group (92.4%) was non-inferior to that in the lansoprazole 30 mg group (91.3%) during the 8-week treatment period.

In Study [TAK-438/CCT-003], results of the primary analysis showed that the EE recurrence rates in vonoprazan 10 mg (5.1%) and 20 mg (2.0%) treatment groups were non-inferior to that in lansoprazole 15 mg (16.8%) treatment group during the 24-week maintenance period.

2.4.2 Safety Results

Most commonly reported adverse events in clinical trials included constipation, diarrhea, abdominal fullness, nausea, rash, increased liver enzymes, edema and eosinophilia.

Post-marketing safety reports included drug hypersensitivity (including anaphylactic shock), hepatotoxicity, Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme.

2.5 Bridging Study Evaluation

The impact of ethnic factor on the PK of vonoprazan was evaluated by cross-study comparison. At the relevant doses of 10 and 20 mg following multiple daily doses for 7 days, the mean Cmax was similar between Caucasian subjects and Japanese subjects; the AUC0-τ

was 29%-32% higher in Caucasian subjects than in Japanese subjects. Overall, there appeared to be no significant ethnic difference in PK of vonoprazan between the Japanese and Caucasian subjects.

These 3 pivotal studies were all conducted in East Asian population, bridging study is not required.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/P D were adequate and acceptable. Three adequate and well controlled studies were provided to demonstrate the efficacy of Vocinti (vonoprazan) for the treatment and maintenance treatment of erosive esophagitis. The overall safety profile was acceptable and post-marketing safety reports disclosed a potential risk of hepatotoxicity. A risk management plan (RMP) is required to ensure that the benefits of the drug outweigh the risks.

3. Post-Marketing Requirements

Routine pharmacovigilance is adequate for post-marketing safety evaluation.
Medication guide and communication plan with emphasis on liver function evaluation are required.