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novugen
Vozan
Vonoprazan

1. NAME OF THE MEDICINAL PRODUCT
Vozan 10mg Film Coated Tablets
Vozan 20mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Vozan 10mg Film Coated Tablets: Each tablet contains 13.361mg of Vonoprazan Fumarate equivalent to 10mg Vonoprazan.
Vozan 20mg Film Coated Tablets: Each tablet contains 26.721mg of Vonoprazan Fumarate equivalent to 20mg Vonoprazan.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.
Vozan 10mg Film Coated Tablets: Yellow, oval shaped tablet with beveled edges, debossed with "H2" on one side and plain on the other side.
Vozan 20mg Film Coated Tablets: Pink, oval shaped tablet, with beveled edges, scored on both side and debossed with "H3" on one side and plain on the other side.

4. CLINICAL PARTICULARS
4.1 Therapeutic 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.

4.2 Posology and Method of 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 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.

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, 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.

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

4.4 Special Warnings and Precautions for Use
Hepatotoxicity
Hepatic function abnormalities including liver injury have been reported. 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 antibiotihcs 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.

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.

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.

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
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
It is unknown whether vonoprazan is excreted in human 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
The influence of Vonoprazan on the ability to drive and use machines is unknown.

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; common; uncommon; rare; very rare; not known.

Table 1. 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 2. 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

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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
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.

Pharmacodynamic effects
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.

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, $AUC_{T,SS}$ 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 [^{14}C] 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, AUC12 and C_{max} of vonoprazan increased by 1.8 times and 1.9 times, respectively, and AUC12 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 C_{max} 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) C_{max} 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.

6. PHARMACEUTICAL PARTICULARS
6.1 List of Excipients
Tablet core:
Mannitol, Microcrystalline cellulose, Hydroxypropyl cellulose, Malic acid, Croscarmellose sodium, Magnesium Stearate

Film coat:
Opadry Complete Film Coating System 03F620167 Yellow (10 mg), Opadry Complete Film Coating System 03F640104 Pink (20 mg)

6.2 Incompatibilities
Not applicable

6.3 Shelf Life
Please refer to the expiry date on the product labels.

6.4 Special Precautions for Storage
Store below 30°C.

6.5 Nature and Content of Container
Clear PVC/Alu blisters of 1x10's, 3x10's, 6x10's, 10x10's, 50x10's and 100x10's tablets packed in the outer carton. Not all pack size will be marketed.

6.6 Special precautions for disposal
No special requirements.

7. MANUFACTURER

Manufactured by:
Novugen Pharma Sdn. Bhd.
No. 27, Jalan Lengkuk Teknologi 2,
Taman Teknologi Enstek Fasa 1,
71760 Bandar Baru Enstek,
Negeri Sembilan, Malaysia.

Product Registration Holder:
Novugen Pharma Sdn. Bhd.
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8. DATE OF REVISION

03/04/2023

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