Davono Leaflet
Size: A5

148mm

210 mm

Davono®

Vonoprazan Tablets

Qualitative and quantitative composition:
Davono 10 mg: Each film coated tablet contains: Vonoprazan Fumarate 10 mg
Davono 20 mg: Each film coated tablet contains: Vonoprazan Fumarate 20 mg
Pharmaceutical form: Film coated tablet
Pharmacology
Pharmacotherapeutic Group: Potassium competitive acid blocker (P-CAB) - antibiotics
ATC code: **A02BC08**
Mechanism of action
Vonoprazan is a potassium competitive acid blocker (P-CAB) and does not require activation by acid. It inhibits H+, K+-ATPase in a reversible and potassium-competitive manner. Vonoprazan has a strong basicity and resides on the acid production site of gastric parietal cells for a long time, thereby inhibiting gastric acid production. Vonoprazan exerts a strong inhibitory effect on formation of mucosal damage in upper part of the gastrointestinal tract. Vonoprazan does not exhibit anti-Helicobacter pylori activity nor inhibitory activity against Helicobacter pylori urease.
Adjunctive effect on eradication of Helicobacter pylori:
The role of Vonoprazan in the Helicobacter pylori eradication is considered to increase intragastric pH leading to the enhancement of antibacterial activity of amoxicillin hydrate, clarithromycin and metronidazole which are concomitantly administered.
Pharmacokinetic properties
Pharmacokinetics at consecutive administration of a daily dose of 10mg or 20mg of Vonoprazan in healthy adult male subjects once daily for 7 days, AUC (0-tau) and Cmax increase as the dose increases. The degree of these increases is slightly higher than the dose ratio. It is considered that the 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.
Absorption
Absolute bioavailability has not been determined. The pharmacokinetic parameters of Vonoprazan following single administration to healthy adult male subjects at 20mg under fasting and fed conditions are presented in the table as follows:

Dose condition	Under fasting	After meal
Tmax (h)	1.5 (0.75, 3.0)	3.0 (1.0, 4.0)
Cmax (ng/ml)	24.3 ± 6.6	26.8 ± 9.6
T1/2 (h)	7.7 ± 1.0	7.7 ± 1.2
AUC(0-tau) (ng.h/ml)	222.1 ± 69.7	238.3 ± 71.1
Mean ± S.D. of 12 subjects [Tmax is expressed by the median (minimum value, maximum value)]		

Distribution
The protein binding rate is 85.2 to 88.0% when [14C] Vonoprazan in the range of 0.1 to 10μg/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).
Elimination
When radioactive-labelled drug (15mg 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 feaces.
Special population
Patients with renal impairment
The effect of renal disorders on pharmacokinetics of Vonoprazan in subjects with normal renal function, patients with mild, moderate, and severe renal disorder and patients with end-stage renal disease (ESRD) when administered the drug as a single dose of Vonoprazan 20mg shows that AUC∞ and Cmax were higher by 1.3 to 2.4 times and 1.2 to
1.8 times, respectively, in patients with mild, moderate, and severe renal disorder compared to subjects with normal renal function, showing an increase with a reduction in renal function. AUC∞ and Cmax were higher by 1.3 times and 1.2 times, respectively, in ESRD patients compared to those in subjects with normal renal function.
Patients with hepatic impairment
The effect of hepatic disorders on pharmacokinetics in subjects with normal hepatic function and patients with mild, moderate and severe hepatic disorder when administered the drug as a single dose of Vonoprazan 20mg shows that AUC∞ and Cmax were higher by 1.2 to 2.6 times and 1.2 to 1.8 times, respectively, in patients with mild, moderate and severe hepatic disorder, compared to subjects with normal hepatic function
Therapeutic indications:
Vonoprazan is indicated for: Gastric ulcer, duodenal ulcer, reflux esophagitis, prevention of recurrence of gastric or duodenal ulcer during low-dose aspirin administration, prevention of recurrence of gastric or duodenal ulcer during non-steroidal anti-inflammatory drug (NSAID) administration.
-Adjunct to Helicobacter pylori eradication in the following settings:
Gastric ulcer, duodenal ulcer, gastric mucosa-associated lymphatic tissue (MALT) lymphoma, idiopathic thrombocytopenic purpura, the stomach after endoscopic resection of early-stage gastric cancer or Helicobacter pylori gastritis.
Posology and method of administration:
Method of administration: Orally with a glass of water.
Reflux oesophagitis
The usual adult dosage is 20 mg of vonoprazan administered orally once daily. The usual treatment period is up to 4 weeks, but it may be extended up to 8 weeks if the efficacy is inadequate. For the maintenance therapy to prevent recurrence or relapse of reflux esophagitis, the dose for oral use is 10 mg or 20 mg once daily.
Gastric ulcer:
-Prevention of recurrent gastric or duodenal ulcer associated with low-dose aspirin administration: The usual adult dosage is 10 mg of vonoprazan administered orally once daily.
-Prevention of recurrent gastric or duodenal ulcer associated with non-steroidal anti-inflammatory drug administration: The usual adult dosage is 10 mg of vonoprazan administered orally once daily.
Contraindications:
Vonoprazan is contraindicated in:
- Patients with hypersensitivity to Vonoprazan or to any excipient of the product.
- Patients receiving atazanavir sulphate, nelfinavir or rilpivirine hydrochloride.

Special warnings and precautions for use:
General
At the treatment, the course of the disease should closely be observed and the minimum therapeutic necessity should be used according to the disease condition.
In the long-term, treatment with Vonoprazan, close observation by such means as endoscopy should be made.
In the maintenance of healing of reflux esophagitis, Vonoprazan should be administered only to the patients who repeat recurrence and recrudescence of the condition. Administration to the patients who do not necessitate maintenance of healing should be avoided.
When the healing is maintained over a long period and when there is no risk of recurrence, the dose reduction to a dose of 10mg from a dose 20mg, or suspension of administration should be considered.
Impaired Renal Function
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.
Impaired Hepatic Function
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. Hepatic function abnormalities including liver injury have been reported. 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.
Pregnancy
Vonoprazan should be used in pregnant women or women having possibilities of being pregnant only if the expected therapeutic benefit is thought to outweigh any possible risk.
Nursing Mothers
It is advisable to avoid the administration of Vonoprazan to nursing mothers. However, when the administration is indispensable, nursing should be discontinued
Interaction with other medicinal products
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 nodose 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.
Fertility, pregnancy and lactation
Pregnancy
No clinical studies have been conducted to date to evaluate vonoprazan in subjects who are pregnant.
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.
Fertility
Animal studies do not indicate direct or indirect harmful effects with respect to male and female fertility
Effects on ability to drive and use machines: no effect on the ability to drive or to use machines
Undesirable effects:
The most commonly reported adverse drug reactions, during controlled clinical trials with rabeprazole were headache, diarrhea, abdominal pain, asthenia, flatulence, rash and dry mouth. The majority of adverse events experienced during clinical studies were mild or moderate in severity, and transient in nature
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
Shelf life: 3 years
Special precautions for storage:
Do not store above 30°C. Protect from direct sunlight.
Keep all medicines out of reach of children.
Nature and contents of container:
Alu-Alu blister packs of 3 ×10's in a unit carton
Distribution category: Prescription Only Medicine (POM).

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