Axavon®
(VONOPRAZAN)

ایگزاوون

FILM COATED TABLETS

فلم کوٹڈ ٹیبلیٹس

QUALITATIVE AND QUANTITATIVE COMPOSITION

Axavon 10 mg Tablet

Each film coated tablet contains:

Vonoprazan Fumarate eq. to Vonoprazan.....10 mg

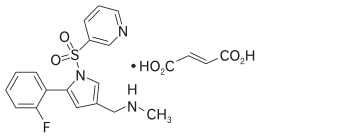
Axavon 20 mg Tablet

Each film coated tablet contains:

Vonoprazan Fumarate eq. to Vonoprazan.....20 mg

DESCRIPTION

Axavon contains Vonoprazan, which is a potassium competitive acid blocker (P-CAB). Chemically, vonoprazan is 1 - [5 - (2-fluorophenyl) - 1 - (pyridin - 3 - ylsulfonyl) - 1H - pyrrol-3-yl] - N - methylmethanamine monofumarate. Its molecular formula is $C_{17}H_{18}FN_3O_2S \bullet C_4H_4O_4$ having molecular weight 461.46 and the structural formula is:



CLINICAL INFORMATION

Indications

- Treatment of gastric ulcer (GU)
- Treatment of duodenal ulcer (DU)
- Treatment of reflux esophagitis (RE) (erosive esophagitis)
- 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
- Prevention of recurrence of gastric ulcer or duodenal ulcer during low dose Aspirin administration
- Adjunct to *Helicobacter pylori* eradication associated with: Gastric ulcer, duodenal ulcer, gastric MALT (mucosa-associated lymphatic tissue) lymphoma, idiopathic thrombocytopenic purpura, the stomach after endoscopic resection of early stage cancer, or *Helicobacter pylori* gastritis

DOSAGE AND ADMINISTRATION

- ***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 hydrate, 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 hydrate, and clarithromycin fails, alternative treatment with the following 3 drugs is recommended;20 mg vonoprazan, 750 mg amoxicillin hydrate, and 250 mg metronidazole, orally administered at the same time twice daily for 7 days.

Administration requirements

Vonoprazan can be taken without regard to food or timing of food.

Contraindications

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

Warning and Precautions

Hepatotoxicity

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.

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, serious colitis, 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.

Fractures

An increased risk for osteoporosis-related fractures of the hip, wrist or spine have been reported in patients under treatment with proton pump inhibitors. The risk of fracture was especially increased in the patients receiving high dose over long term period (>1 year) treatment. The mechanism is not clear and is likely to be multifactorial.

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.

Use in elderly

Since the physiological functions such as hepatic or renal function are decreased in elderly patients in general, vonoprazan should be carefully administered.

Use in children

Vonoprazan has not been studied in patients under 18 years of age.

Drug Interactions

- Use of vonoprazan is not recommended with drugs for which absorption is dependent on acidic intragastric pH such as atazanavir and nelfinavir, due to significant reduction in their bioavailability
- Blood concentration of vonoprazan increased in concomitant use with clarithromycin
- Coadministration of vonoprazan with the antibiotic regimen clarithromycin and amoxicillin increased concentrations of vonoprazan by up to 1.9 fold

Pregnancy and Breastfeeding

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. Nursing should be avoided if the administration of this drug is necessary for the mother.

Adverse Reactions

Common	Uncommon	Unknown
Diarrhea, Constipation	Nausea, Abdominal distention	Urticaria, Rash, Hepatotoxicity, Jaundice, Drug eruption

Overdose
Vonoprazan is not removed from the circulation by hemodialysis.
If overdose occurs, treatment should be symptomatic and supportive.

PHARMACOLOGICAL PROPERTIES
Pharmacotherapeutic group
Potassium competitive acid blocker (P-CAB)

Mechanism of Action
Vonoprazan is a potassium competitive acid blocker (P-CAB) 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.

Pharmacokinetic properties
At consecutive administration of a daily doses of 10 - 40 mg of vonoprazan in healthy adult male subjects once daily for 7 days, $AUC_{\tau,ss}$ and $C_{max,ss}$ increase in a slightly greater than dose proportional manner. Steady state is achieved 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. Vonoprazan does not exhibit time-dependent pharmacokinetics. The following table shows pharmacokinetic parameters of vonoprazan on day 7 of administration.

Dose condition	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
$AUC_{\tau,ss}$ (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 to healthy adult male subjects at 20 mg under fasting and fed conditions are presented in the table as follows:

Dose condition	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 ± S.D. 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.

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
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 has been evaluated in individuals 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_{∞} is increased by 1.3 to 2.4 times and the C_{max} by 1.2 to 1.8 times, in patients with mild, moderate or severe renal disorder compared to normal renal function indicating an increase in vonoprazan exposure with a reduction in renal function. The AUC_{∞} is higher by 1.3 times and the C_{max} higher by 1.2 times in ESRD patients compared to those with normal renal function.

Impaired Hepatic Function: The effect of hepatic disorders on pharmacokinetics of vonoprazan has been evaluated in individuals with normal hepatic function and patients with mild, moderate or severe hepatic disorder. When administered a single dose of vonoprazan 20 mg, the AUC_{∞} is increased by 1.2 to 2.6 times and C_{max} by 1.2 to 1.8 times in patients with mild, moderate or severe hepatic disorder compared to those with normal hepatic function.

PHARMACEUTICAL INFORMATION
Shelf life
2 Years

Instructions
To be sold on the prescription of a registered medical practitioner only.
Do not store above 30°C.
Protect from light and moisture.
Keep out of the reach of children.

ہدایات :
صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔
۳۰ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں۔
دوا کو روشنی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

Nature and contents of container
Axavon 10 mg tablet are available in blister pack of 14's.
Axavon 20 mg tablet are available in blister pack of 14's.

MANUFACTURED BY:
Aspin Pharma (Pvt.) Ltd.
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www.aspin.com.pk

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