SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DAVONO 20 MG Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Vonoprazan Fumarate 20 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vonoprazan is indicated for:

- Gastric ulcer.
- Duodenal ulcer.
- Reflux oesophagitis.
- 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.

4.2 Posology and method of administration

Posology

Reflux oesophagitis

Adults:

20 mg once daily for 4 weeks, which may be followed by a further 4 weeks if necessary.

Maintenance therapy of healing in patients with repeat recurrence.

Gastric ulcer

Adults:

20 mg once daily for 8 weeks.

Method of administration

For oral administration.

The tablets should be taken orally with a glass of water.

4.3 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.

4.4 Special warnings and precautions for use

General

During treatment, the course of the disease should be closely 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 oesophagitis, vonoprazan should be administered only to patients who repeatedly experience recurrence and recrudescence of the condition. Administration to 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, dose reduction to 10 mg from a dose of 20 mg, 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.

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

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 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.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to male and female fertility.

4.7 Effects on ability to drive and use machines

Based on the pharmacodynamic properties and the adverse events profile, it is unlikely that vonoprazan would cause an impairment of driving performance or compromise the ability to use machinery.

If, however, alertness is impaired due to somnolence, it is recommended that driving and operating complex machinery be avoided.

4.8 Undesirable effects

The most commonly reported adverse drug reactions, during controlled clinical trials with rabeprazole were headache, diarrhoea, 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the National Regulatory Authority.

4.9 Overdose
There is no experience of overdose with vonoprazan.

Vonoprazan is not removed from the circulation by haemodialysis.

If overdose occurs, treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Potassium competitive acid blocker (P-CAB)
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.

5.2 Pharmacokinetic properties

Pharmacokinetics at consecutive administration of a daily dose of 10 mg or 20 mg 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.

In addition, it is considered that pharmacokinetics of vonoprazan at consecutive administration may not be time-dependent, as the result of the evaluation of accumulation with regard to AUC(0-tau) and T1/2 of vonoprazan.

Dose condition	**20mg**
Tmax (h)	1.5 (0.75, 3.0)
Cmax (ng/ml)	26.3 ± 6.6
T1/2 (h)	6.1 ± 1.2

AUC(0-tau) (mg h/ml)	151.6 ± 40.3

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 as follows:

Pharmacokinetic parameter	Under fasting	After meal
Tmax (h)	1.5 (0.75, 3.0)	2.30 (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) (mg h/ml)	222.1 ± 69.7	238.3 ± 71.1

Distribution

The protein 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.

Elimination

When radioactive-labelled 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

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 20 mg 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 a single dose of vonoprazan 20 mg 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.

5.3 Preclinical 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.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Mannitol
- Microcrystalline Cellulose PH 101
- Hydroxypropyl Cellulose
- Croscarmellose Sodium

- Polyvinylpyrrolidone K30
- Fumaric acid
- Magnesium stearate
- Microcrystalline Cellulose PH 102
- Colloidal Anhydrous Silica (Aerosil)
- Ready Coat AQ Brown
- Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30 °C.

Protect from direct sunlight.

Keep all medicines out of reach of children.

6.5 Nature and contents of container

Alu-Alu blister pack of 2 × 10's, packed in printed unit carton with literature insert.

6.6 Special precautions for disposal and other handling

This medicinal product does not require any special storage conditions.

7. Marketing Authorisation Holder
Dawa Limited
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Manufactured by:

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8. Marketing Authorisation Number
H2024/CTD11636/24588

9. Date of First Authorisation / Renewal of Authorisation
2024 September 16

10. Date of Revision of The Text
2024 September 16