

FEXUPRAZAN HCl

FEXUCLUE®

40mg Film-coated Tablet

Potassium-Competitive Acid Blocker (P-CAB)

Rx

Formulation

Each tablet contains:

- Active Pharmaceutical Ingredient Fexuprazan HCl 40 mg
- Additives (animal-derived ingredients): lactose hydrate (bovine, milk)
- Additives (tar dye): Yellow No.4
- Other additives: Microcrystalline Cellulose, Magnesium stearate, Opadry Green AMB2 88A610038, Opadry White 03B28796, Croscarmellose Sodium, Yellow Iron Oxide.

Product Description

Pale-green, oblong film-coated tablet with the breaking line on the tablet.

Pharmacokinetics and Pharmacodynamics

1. Pharmacological actions

The product has a mechanism of action to inhibit gastric acid secretion by controlling H⁺/K⁺ - ATPase in parietal cells of the stomach in a K⁺ ion-dependent and reversible manner. The product directly inhibits the proton pump without undergoing acid-induced activity.

2. Pharmacokinetic studies

1) Absorption

When a single administration of 10~320 mg of the product was carried out in healthy adults, it was rapidly absorbed and the maximum plasma concentration reached a median value of 1.75~3.5 hours after administration. Blood drug concentration increased as the dose increased. When 20~160 mg of the product was repeatedly administered orally for 7 days, the drug concentration in the steady state and the terminal elimination half-life were similar to that of the single administration. There was no accumulation of in vivo exposure after repeated administration and the drug concentration in blood tended to increase in proportion to the increase in dose.

As a result of orally administering 160 mg of the product to healthy adult males after fasting and high-fat diet to evaluate the dietary effect on bioavailability, there were no significant differences in in vivo exposure and pharmacodynamic endpoints (retention time above pH 4 in the stomach).

2) Distribution

The in vitro plasma protein binding rates in human plasma were 94.3% and 92.8% at concentrations of 1 and 10 µg/mL, respectively.

3) Metabolism

The product is mainly metabolized by CYP3A4. The main metabolite is metabolite M14 and this metabolite is ineffective.

4) Excretion

The amounts of unchanged forms excreted from urine and feces after intravenous administration in rats were 0.61% and 34.22%, respectively. After oral administration of the 14C marker product to rats, the excretion recovery rate at 120 hours was 98.9%, where the recovery rates of urine and feces were 18.8% and 80.1%, respectively. After single oral administration to biliary tract intubated rats, the bile was excreted at 88.0% at 48 hours and the total recovery rate was 98.2%. After oral administration of the 14C marker product to dogs, the fecal recovery rate at 168 hours was 96.7%, while the recovery rates of urine and feces were 38.8% and 57.9%, respectively.

After oral administration of the product to healthy adult males, the mean elimination half-life of unchanged forms and metabolite M14 were 9.7 hours and 14.2 hours, respectively. The urine

excretions and elimination rate of the unchanged form were about 0.6% and 0.63 L/hr, respectively.

5) Drug -Drug Interaction

(1) Drugs that may affect the plasma concentration of the product

① The product is a substrate of CYP3A4 and when the product and a CYP3A4 inhibitor were administered in combination, the increase in exposure to the product may be slight.

The AUCt (Area under the plasma concentration-time curve from time zero to time t) of the product increased slightly by 1.1 times as a result of co-administration of 80 mg of the product and 500 mg as clarithromycin twice a day for 7 days in healthy adult males.

(2) Drugs whose plasma concentration may be changed by the product

① The product showed competitive inhibitory effect against CYP3A4 in in vitro, but its IC50 (11.7 μ M) was about 100 times higher than the maximum plasma concentration in the clinical dose (40mg basis).

② As a result of co-administration of three preparations, 80 mg of the product, 1 g as amoxicillin and 500 mg as clarithromycin twice a day for 7 days to healthy adult males, the AUCT and C_{ss,max} of clarithromycin were decreased to 23% and 28%, respectively and the AUCT and C_{ss,max} of amoxicillin were decreased to 14% and 33%, respectively.

③ The product showed competitive inhibitory effect against MATE1, MATE2K and OCT1 in in vitro, but it is unlikely to increase the blood concentration of the transporter substrate drug when considering the maximum plasma concentration at the clinical dose (40 mg basis).

Indication

Treatment of erosive esophagitis (EE)

Dosage and Administration

The product is administered to adults as follows.

- Treatment of erosive esophagitis (EE)
 - 40 mg is administered orally once a day for 4 weeks.
 - In the case of patients with untreated esophagitis or persisting symptoms, the administration is given for another 4 weeks. The product can be administered with or without meals.

Precautions for Use

1. Contraindications

- 1) Patients who have a history of hypersensitivity to the product or its components
- 2) Patients taking a drug containing atazanavir, nelfinavir, or rilpivirine (refer to 5. Interactions)
- 3) Pregnant and lactating women (refer to 6. Administration to Pregnant and Lactating Women)
- 4) Patients who have congenital conditions for lactose such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption, as this medicine contains lactose

2. In the following patients, Fexuprazan should be administered with care.

- 1) Patients with hepatic impairment (no experience of use)
- 2) Patients with renal impairment (no experience of use)
- 3) Elderly (refer to 8. Geriatric Use)
- 4) Patients who have a history of hypersensitivity or allergy to Yellow 4 Tartrazine

3. Adverse Event

A total of two clinical trials were conducted in patients with erosive esophagitis (EE). Of the subjects who participated in the clinical trials, 183 received 40 mg of the product. Adverse events reported in clinical trials are as follow. Adverse events (1% or more) and adverse drug reactions (*) commonly reported in the product administration group are shown in the following Table 1.

Table 1. Adverse events reported by 1% or more in clinical trials

System Organ Class (SOC)	Adverse Event
Gastrointestinal disorders	Indigestion*, diarrhea*, nausea*, abdominal discomfort*, chronic gastritis, gastritis, erosive gastritis
Skin and subcutaneous tissue disorders	Erythema*
Nervous system disorders	Headache*
Musculoskeletal and connective tissue disorders	Low back pain

Other adverse events reported in clinical trials with an incidence of less than 1% after administration of the product are listed according to the major system organ class as follows.

- Gastrointestinal disorders: Hiatal hernia, Brunner's gland hyperplasia
- Infections and infestations: Bronchitis, herpes simplex, influenza, periodontitis, pharyngitis, vaginal infections
- Skin and subcutaneous tissue disorders: Contact dermatitis, pruritus*, systemic pruritus*, facial edema
- General disorders and administration site conditions: Chest discomfort, strange feeling*, edema, pain, fever
- Nervous system disorders: Dizziness, dysgeusia
- Musculoskeletal and connective tissue disorders: Myalgia*, musculoskeletal pain, neck pain
- Eye disorders: Cataract, septum bleeding*, retinal laceration
- Ear and labyrinth disorders: Ear discomfort*
- Respiratory, thoracic and mediastinal disorders: Runny nose
- Metabolic and nutritional disorders: Hypertriglyceridemia

4. General Cautions

1) Since the product may relieve symptoms of malignant tumors or delay the diagnosis, if a malignant tumor is suspected by warning symptoms (unintended significant weight loss, recurrent vomiting, dysphagia, hemoptysis, melena, etc.) and a gastric ulcer is present or suspected, it should be administered after confirming that it is not malignant.

2) The number of bacteria usually present in the gastrointestinal tract increases when acidity in the stomach decreases due to proton pump inhibitors (PPIs). The risk of infection of the gastrointestinal tract by bacteria such as Salmonella, Campylobacter and Clostridium difficile may slightly increase when treated with gastric acid inhibitors. This is associated with an increased risk of Clostridium difficile diarrhea and several observational studies have reported that this risk is increased, especially in hospitalized patients. This diagnosis should be considered when diarrhea does not improve. Clostridium difficile diarrhea has been reported with the use of almost all antimicrobial agents.

3) Proton Pump Inhibitor (PPI) treatment has been reported to have the potential of being associated with an increased risk of osteoporosis-related fractures of the hip, wrist and spine. The risk of fracture was increased in patients receiving high doses of PPIs (defined as repeated daily administration) and in patients with long-term use longer than a year.

In the case of patients at risk of developing osteoporosis and osteoporotic fractures, appropriate clinical monitoring is recommended according to the latest clinical guidelines.

4) Hypomagnesemia was rarely reported in patients who had been under treatment with a proton pump inhibitor (PPI) for more than 3 months and were most frequent cases were treated for more than a year. In most patients, treatment of hypomagnesemia requires magnesium supplementation and discontinuation of PPI. Patients requiring long-term treatment or co-administering digoxin or drugs that cause hypomagnesemia (e.g., diuretics) require periodic monitoring of magnesium levels, including at the initiation of treatment. Serious adverse events include stiffness, arrhythmia, and seizures.

5) Increase of serum gastrin was reported in patients who had been under the treatment with a proton pump inhibitor(PPI). Increased gastrin can cause enterochromaffin-like cell hyperplasia

and increased serum Chromogranin A (CgA) levels. The increased CgA levels may cause false positive results in diagnostic investigations for neuroendocrine tumors.

5. Interactions

1) Since the administration of the product raises the pH in the stomach, it can interact with drug absorption in the case of oral drugs, where the pH of the stomach is an important determinant of bioavailability. Therefore, the use of the product may reduce the bioavailability of drugs that depends on the gastric pH, such as atazanavir and nelfinavir.

2) The product is mainly metabolized by CYP3A4 and partially by CYP2B6, CYP2C19 and CYP2D6.

3) When 80 mg of the product and clarithromycin were co-administered, the AUC_t of the product and clarithromycin were shown to be 1.1 times and 0.77 times, respectively, which were not clinically significant.

4) When the product, clarithromycin and amoxicillin were co-administered, the AUC_t of amoxicillin was shown to be 0.86 times, but it was not clinically significant.

6. Use in Pregnant and Lactating Women

1) Pregnant women

There are no clinical trial data of the product in pregnant and lactating women. As a result of embryo-fetal development tests in rats and rabbits, maternal body weight and feed intake decreased, but there was no effect on embryo-fetal development. For safety reasons, the use of the product during pregnancy is prohibited.

2) Lactating women

Breastfeeding should be discontinued if the product is used as it is not known if the product will pass to breast milk in lactating women. In animal studies (rats), it has been reported that the product passes into breast milk.

7. Pediatric Use

The clinical safety and efficacy of the product in children and adolescents have not been established.

8. Geriatric Use

In general, physiological functions such as hepatic functions or renal functions tend to decline in the elderly, so it should be administered carefully.

9. Use in Patients with Renal Impairment

The safety and efficacy of the product in patients with renal impairment **have not been** established.

10. Use in Patients with Hepatic Impairment

The safety and efficacy of the product in patients with hepatic impairment have not been established.

11. Treatment in Case of Overdose

No cases of severe overdose of the product have been reported. In clinical trials, there has been an experience of single dose of the product up to 320 mg. In the event of overdose, the patient should be monitored for symptoms of toxicity and if necessary, general adjuvant treatment should be provided.

12. Precautions for Storage and Handling

1) Keep out of reach of children.

2) Be aware that transferring it to another container may cause an accident or is not desirable in terms of quality maintenance.

13. Information for Professionals

1) Clinical studies

(1) Erosive esophagitis

A randomized, double-blind, comparative phase 3 clinical trial with 40 mg of the product or 40 mg of Esomeprazole administered orally once daily for up to 8 weeks was conducted in 218 patients with erosive esophagitis. As a study result, the cumulative healing rate at Week 8 is shown in the table below and the non-inferiority of the product to esomeprazole group was confirmed (Table 2).

Table 2. Cumulative healing rate at Week 8 in patients with erosive esophagitis (PPS; Per Protocol Set)*

	Product 40 mg (N=107)	Esomeprazole 40 mg (N=111)
Cumulative Healing Rate n (%)	106(99.07)	110(99.10)
	0.89a) [-0.86, 2.64]b) 0.3378c)	

a) Healing rate difference, % (baseline LA grade correction, Cochran-Mantel-Haenszel Method)

b) 95% confidence interval of healing rate difference, c) p-value

* Non-inferiority margin: -10%

** Study number: DW_DWP14012301

2) Toxicology studies

(1) Genotoxicity

The product was negative in all of the bacterial reverse mutation tests using Salmonella and E. coli, chromosomal abnormality tests using CHO cell lines and micronucleus tests using rats.

(2) Reproductive toxicity

As a result of fertility and early embryo development tests in rats, there was no effect on fertility and early embryo development up to a dose of 50 mg/kg/day.

As a result of the embryo-fetal development test in rats, a decrease in feed intake and weight was observed in the group administered with more than 30 mg/kg/day. The weight of the fetus decreased by 5%, but there was no effect on development or growth delay. The no-effect levels (NOELs) of embryo-fetal and the maternal were confirmed to be 60 mg/kg/day (about 19.8 times the clinical dose of 40 mg AUC) and 15 mg/kg/day (7.5 times the clinical dose 40 mg AUC), respectively. As a result of the embryo-fetal development test in rabbits, a decrease in feed intake and weight and constipation symptoms were observed in the group administered with more than 15 mg/kg/day. However, there was no effect on development or growth delay. The no-effect levels (NOELs) of the maternal and embryo-fetal were confirmed to be 10 mg/kg/day (0.6 times the clinical dose of 40 mg AUC) and 15 mg/kg/day (1.7 times the clinical dose 40 mg AUC), respectively.

As a result of prenatal development and maternal function evaluation tests in rats, there was no effect on the offspring immediately after childbirth by the product, but it was transferred to maternal milk and the body weight decreased during the breastfeeding period in the administration dose of more than 7.5 mg/kg/day (3.7 times the clinical dose 40 mg AUC).

However, no dysfunctions including behavior, development, sexual maturity and genital organs of the offspring even at the high dose of 30 mg/kg/day (17.2 times the clinical dose 40 mg AUC).

(3) Carcinogenicity

In a carcinogenicity study administered orally in rats for 2 years, gastric neuroendocrine tumors were observed at 10mg/kg/day (about 3.7 times based on the clinical dose 40mg/day AUC) for males and 5mg/kg/day (about 4.1 times based on the clinical dose 40mg/day AUC) for females. In the 26-week carcinogenicity test in RasH2 mice, gastric benign adenomas were observed at 60mg/kg/day in males (about 26.9 times based on the clinical dose 40mg/day AUC).

Caution

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.

Seek advice from a healthcare professional at the first sign of any adverse reaction.

Storage Condition:

Store at temperatures not exceeding 30°C

Shelf-life

24 Months

Availability

Alu-Alu/PVC/Nylon blister pack x 7's (Box of 28's)

FDA Registration No.: DR-XY48448

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