CONTRAINDICATIONS (Gaster® D Tablets is contra-indicated in the following patients.)
 Patients with a history of drug hypersensitivity to any of the ingredients in the product

**DESCRIPTION**

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Gaster® D Tablets 10 mg</th>
<th>Gaster® D Tablets 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>(JP) Famotidine 10 mg</td>
<td>(JP) Famotidine 20 mg</td>
</tr>
<tr>
<td>(Content per tablet)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosage form (mm)</td>
<td>Orally disintegrating</td>
<td>Orally disintegrating</td>
</tr>
<tr>
<td></td>
<td>tablet Diameter 7.5</td>
<td>tablet Diameter 8.5</td>
</tr>
<tr>
<td></td>
<td>Thickness 3.1</td>
<td>Thickness 3.6</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>0.12</td>
<td>0.18</td>
</tr>
<tr>
<td>Color</td>
<td>White</td>
<td></td>
</tr>
<tr>
<td>Identification Code</td>
<td>▲120</td>
<td>▲121</td>
</tr>
</tbody>
</table>

Additives: Ethylcellulose, cetanol, sodium laurylsulfate, triacetin, cyclodextrin, aroma chemical, D-mannitol, aspartheme (L-phenylalanine), maltose syrup powder, calcium stearate.
Gaster® D Tablets 20 mg also contains l-menthol.

**INDICATIONS**

- Gastric ulcers, duodenal ulcers, anastomotic ulcers, upper gastrointestinal hemorrhage (associated with peptic ulcers, acute stress-induced ulcers and hemorrhagic gastritis), reflux esophagitis and Zollinger-Ellison syndrome.

**DOSAGE AND ADMINISTRATION**

- Gastric ulcers, duodenal ulcers, anastomotic ulcers, upper gastrointestinal hemorrhage (associated with peptic ulcers, acute stress-induced ulcers and hemorrhagic gastritis), reflux esophagitis and Zollinger-Ellison syndrome
For adults, the usual dosage is 20 mg of famotidine orally administered twice a day, once after breakfast and once after the evening meal or before sleeping; or 40 mg of famotidine orally administered once a day before sleeping. The dosage may be adjusted according to the patient's age and symptoms. For upper gastrointestinal hemorrhage, the drug should first be given by injection, and then oral doses should be substituted when the patient is able to take the drug orally.

- Gastric mucosal lesions (erosion, hemorrhage, redness or edema) associated with acute gastritis, and acute exacerbation of chronic gastritis
For adults, the usual dosage is 10 mg of famotidine orally administered twice a day, once after breakfast and once after the evening meal or before sleeping; or 20 mg of famotidine orally administered once a day before sleeping. The dosage may be adjusted according to the patient's age and symptoms.

**Administration to patients with impaired renal function**
Famotidine is mainly excreted by the kidneys in the form of unchanged drug. Thus, administration of famotidine to patients with impaired renal function results in an increase in blood concentration of unchanged drug and a decrease in urinary excretion. The following dosage is therefore recommended in patients with impaired renal function:

<table>
<thead>
<tr>
<th>Creatinine clearance (mL/min)</th>
<th>Recommended dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ccr ≥ 60</td>
<td>20 mg, twice daily</td>
</tr>
</tbody>
</table>
PRECAUTIONS

1. Careful Administration (Gaster®D Tablets should be administered with care in the following patients.)
   (1) Patients with a history of drug hypersensitivity
   (2) Patients with impaired renal function [As a high level of drug concentration in the blood may persist, it is advisable to take such measures as a reduction in the dose or a prolongation of the administration interval.]
   (3) Patients with cardiac disorders [This drug may cause cardiovascular adverse reactions.]
   (4) Patients with impaired hepatic function [Symptoms may be exacerbated.]
   (5) The elderly [See “Use in the Elderly”.]

2. Important Precautions
   (1) Although the drug disintegrates in the oral cavity, the tablets should be swallowed with saliva or water since the drug is not absorbed from the mucosa of the oral cavity.
   (2) Patients should be carefully observed during treatment, and the minimum required dose should be used according to symptoms. If response is not evident, other treatments should be implemented. Careful observation should be made for any changes in hematological, hepatic or renal parameters, and for changes in other factors.

3. Drug Interactions
   [Precautions for coadministration] (Gaster®D Tablets should be coadministered with care when coadministered with the following drugs.)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Signs, Symptoms, and Treatment</th>
<th>Mechanism and Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azole antifungal agents such as itraconazole</td>
<td>Famotidine may decrease blood concentrations of azole antifungal agents with concomitant administration.</td>
<td>The inhibitory action of famotidine on gastric acid secretion decreases the rate of oral absorption of itraconazole.</td>
</tr>
</tbody>
</table>

4. Adverse Reactions
   Adverse reactions (including abnormal changes in laboratory tests), which were suspected of being related to famotidine, appeared in 360 (1.8%) of 20,137 cases, which included both oral and intravenous administration routes, and studies at the time of approval and during the period of post-marketing surveillance. The main adverse reactions were constipation and decrease of leukocytes (at the time of approval of orally disintegrating tablets).

(1) Clinically significant adverse reactions
   1) Shock or anaphylactic reactions (< 0.1%): Symptoms of anaphylactic shock, such as dyspnea, generalized erythema, vascular edema (facial edema, pharyngeal edema, etc.), and urticaria may occur rarely. Patients should be carefully observed, and if signs of these conditions develop, administration should be discontinued immediately and appropriate treatment should be administered.
   2) Pancytopenia, agranulocytosis, aplastic anemia, and hemolytic anemia (Incidence unknown): Pancytopenia, agranulocytosis, aplastic anemia, and hemolytic anemia may occur. If symptoms such as generalized fatigue, weakness, subcutaneous or submucosal hemorrhage, or fever occur, periodic hematologic tests should be conducted. If results show hematologic complications, administration should be discontinued immediately and appropriate treatment should be administered.
   3) Muco-cutaneo-ocular syndrome (Stevens-Johnson syndrome) and toxic epidermal necrolysis (Lyell’s syndrome) (Incidence unknown): Muco-cutaneo-ocular syndrome (Stevens-Johnson syndrome) or toxic epidermal necrolysis (Lyell’s syndrome) may occur. Patients should be carefully observed, and if signs of these conditions develop, administration should be discontinued immediately and appropriate treatment should be administered.
   4) Hepatic function disorder and jaundice (Incidence unknown): Elevation of AST (GOT), ATL (GPT), and other liver enzyme levels, and jaundice may occur. Patients should be carefully observed, and if signs of these conditions develop, administration should be discontinued immediately and appropriate treatment should be administered.
   5) Rhabdomyolysis (Incidence unknown): Rhabdomyolysis may occur. If hyperkalaemia, myoglobinuria, marked increase of muscle-specific enzyme levels in serum, and myalgia are noted, administration should be discontinued immediately and appropriate treatment should be administered.
   6) Prolonged QT interval (Incidence unknown): Prolongation of the QT interval may occur. Patients should be carefully observed, and if signs of these conditions develop, administration should be discontinued immediately and appropriate treatment should be administered. This symptom is especially likely to occur in patients with cardiac disorders such as myocardial infarction, valvular disease, and cardiomyopathy, therefore the patient’s condition must be closely monitored after drug administration.
   7) Impaired consciousness and convulsions (Incidence unknown): Impaired consciousness or generalized convulsions (clonic, spastic, myoclonic) may occur. Patients should be carefully observed, and if signs of these conditions develop, administration should be discontinued and appropriate treatment should be administered. This symptom is especially likely to
occur in patients with impaired renal function, therefore caution should be taken.

8) **Interstitial nephritis and acute renal failure** (Incidence unknown): Interstitial nephritis or acute renal failure may occur. If fever, eruption, or abnormal renal function (increase in BUN or creatinine) is noted at an early stage, administration should be discontinued immediately and appropriate treatment should be administered.

9) **Interstitial pneumonia** (Incidence unknown): Interstitial pneumonia accompanied by fever, cough, dyspnea, or chest X-ray abnormalities may occur. If such symptoms appear, administration should be discontinued immediately, and appropriate treatment, such as corticosteroid therapy, should be administered.

(2) Clinically significant adverse reactions (Analog)

*Asystolia:* It has been reported that asystolia may occur with other H₂-receptor antagonists.

(3) Other adverse reactions

<table>
<thead>
<tr>
<th>Larbenity</th>
<th>5% &gt; 0.1%</th>
<th>&lt;0.1%</th>
<th>Incidence unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematolo-gical</td>
<td>Decrease of leukocytes</td>
<td>Decrease of platelets, increase of eosinophils</td>
<td></td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>Constipation</td>
<td>Diarrhea/ loose stools, thirst, nausea/vomiting, feeling of enlarged abdomen, decreased appetite, stomatitis, etc.</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Increase in blood pressure, facial hot flushes, tinnitus</td>
<td>Bradycardia, tachycardia, atrioventricular block</td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>Elevation of AST (GOT), elevation of ALT (GPT), elevation of Al-P</td>
<td>Elevation of total bilirubin, elevation of LDH</td>
<td>Abnormality in hepatic function, jaundice</td>
</tr>
<tr>
<td>Psychoneurologic</td>
<td>Generalized fatigue/ enervation, headache, sleepiness, insomnia</td>
<td>Reversible confusion, depression, convulsion, disorder in consciousness</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>Menstrual irregularity, gynecomastia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note1) If these signs are noted, administration should be discontinued.

Note2) Data based on voluntary reports from patients

5. Use in the Elderly

This drug should be administered with care, e.g. a reduction in the dose and a prolongation of the administration interval. [This drug is mainly excreted by the kidneys. Elderly patients may have renal hypofunction, and high blood concentrations may persist.]

6. Use during Pregnancy, Delivery or Lactation

1) Administration of this drug to pregnant women or women who may possibly be pregnant should be strictly limited to occasions where the therapeutic benefits outweigh the possible risks associated with the treatment. [The safety of this drug in pregnant women has not been established.]

2) Nursing mothers should discontinue breast feeding during treatment. [It has been reported that the drug is excreted in breast milk.]

7. Pediatric Use

Safety of this product in prematures, newborns, sucklings, infants, and children has not been established.

8. Precautions concerning Use

(1) Cautions in dispensing

Patients should be advised to press the tablet out of the press-through package (PTP) before taking it. (A case has been reported where a patient mistakenly ingested a small angular piece of the PTP sheet, which lodged in the esophageal mucosa and caused perforation and subsequent mediastinitis.)

(2) Cautions in administration

1) The tablet can be soaked with saliva on the tongue and lightly mashed between the tongue and hard palate, and then swallowed with the use of saliva alone.

2) The tablet should not be taken without water if the patient is in a lying down position.

9. Other Precautions

Since treatment with this product may mask the symptoms of gastric cancer, administration should be made after confirming that there is no malignant tumor.

**PHARMACOKINETICS**

1. **Blood concentration**

When 20 mg of Gaster®D Tablets or Gaster®OD Tablets are orally administered to humans, the plasma concentration of unchanged drug reaches a maximum at approximately 3 h after administration. The half-life is approximately 3 h.
and gastric mucosal lesions in acute and chronic gastritis, using Gaster® in the form of tablets, powder, and OD tablets, and the usefulness of the drugs was confirmed.

<table>
<thead>
<tr>
<th>Dosage (mg)</th>
<th>General Improvement rate</th>
<th>Improvement rate of subjective/objective symptoms</th>
<th>Cure/Improvement rate by endoscopic judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Gastric ulcer 4&lt;sup&gt;a&lt;/sup&gt; 20 mg x 2/day</td>
<td>95.2% (1174/1233)</td>
<td>95.1% (1105/1162)</td>
<td>84.1% (1037/1233)</td>
</tr>
<tr>
<td>40 mg x 1/day</td>
<td>98.2% (449/457)</td>
<td>95.4% (412/423)</td>
<td>80.1% (366/457)</td>
</tr>
<tr>
<td>2. Duodenal ulcer 5&lt;sup&gt;b&lt;/sup&gt; 20 mg x 2/day</td>
<td>95.7% (645/674)</td>
<td>95.4% (600/629)</td>
<td>84.6% (582/674)</td>
</tr>
<tr>
<td>40 mg x 1/day</td>
<td>98.8% (343/358)</td>
<td>95.2% (320/336)</td>
<td>86.0% (308/358)</td>
</tr>
<tr>
<td>3. Gastric duodenal ulcers 40 mg x 1/day</td>
<td>100.0% (5/5)</td>
<td>100.0% (5/5)</td>
<td>100.0% (5/5)</td>
</tr>
<tr>
<td>4. Stomal ulcer 20 mg x 2/day</td>
<td>95.7% (22/23)</td>
<td>100.0% (21/21)</td>
<td>87.0% (20/23)</td>
</tr>
<tr>
<td>40 mg x 1/day</td>
<td>75.0% (3/4)</td>
<td>66.7% (2/3)</td>
<td>75.0% (3/4)</td>
</tr>
<tr>
<td>5. Reflux esophagitis 20 mg x 2/day</td>
<td>90.5% (19/21)</td>
<td>90.0% (18/20)</td>
<td>90.5% (19/21)</td>
</tr>
<tr>
<td>40 mg x 1/day</td>
<td>87.5% (21/24)</td>
<td>87.0% (20/23)</td>
<td>83.3% (20/24)</td>
</tr>
<tr>
<td>6. Gastric mucosal lesions in acute and chronic gastritis 10 mg x 2/day</td>
<td>84.1% (333/396)</td>
<td>84.4% (335/397)</td>
<td>81.8% (320/391)</td>
</tr>
<tr>
<td>20 mg x 1/day</td>
<td>81.0% (141/174)</td>
<td>84.0% (142/169)</td>
<td>80.3% (139/173)</td>
</tr>
<tr>
<td>7. Hemostatic effects:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper gastrointestinal hemorrhage</td>
<td>Hemostatic effects by intravenous injection were observed in 91.2% (165/181), and this drug was confirmed to be useful in a double-blind comparative study.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemostatic effects by intravenous administration (20 mg twice a day) in the dose-finding and double-blind comparative studies were obtained in 91.0% (91/100), and the hemostatic rate within 36 hr of administration was 66.0% (66/100). The hemostatic rate within 3 days was 84.0% (84/100).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemostatic maintenance effects:</td>
<td>The hemostatic maintenance effects by oral administration (20 mg twice daily) after hemostasis by intravenous administration were effective.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Zollinger-Ellison syndrome</td>
<td>In an open study on 6 patients (5 for p.o. and 1 for i.v.), effects were obtained in 5 patients (4 for p.o. and 1 for i.v.).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<Parameters when Gaster® Injections 20 mg is administered intravenously>

- 5. Bioequivalence<sup>4,5</sup>
  When Gaster® Tablets, Gaster®OD Tablets, or Gaster®D Tablets are orally administered to humans, the change in blood concentration curves is almost the same, and therefore the formulations are bioequivalent.

**CLINICAL STUDIES**

- 6. Excretion<sup>5,6</sup>
  The excretion rate of unchanged drug in the urine to 24 hr after administration is 21.0% to 49.0% for oral administration, 71.0% to 89.6% for intramuscular administration, and 57.8% to 96.4% for intravenous administration.

- 7. Pharmacokinetic parameters in clinical dosage

<table>
<thead>
<tr>
<th>Dosage (mg)</th>
<th>Tmax (hr)</th>
<th>Cmax (ng/mL)</th>
<th>t1/2 (hr)</th>
<th>AUC (ng·hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OD Tablets</td>
<td>20</td>
<td>2.9</td>
<td>67.1</td>
<td>2.85</td>
</tr>
<tr>
<td>D Tablets</td>
<td>20</td>
<td>3.1</td>
<td>63.4</td>
<td>3.06</td>
</tr>
</tbody>
</table>

- 8. Clinical efficacy<sup>3,24</sup>
  Clinical trials, including double-blind comparative studies, were conducted in patients with gastric ulcers, duodenal ulcers,
PHARMACOLOGY

1. Effects on humans

(1) Inhibition of gastric acid and pepsin secretion

Basic secretion and secretion in response to various stimulants were inhibited at 2 hr after oral administration of 20 mg of famotidine to healthy adults and to patients with peptic ulcers. Gastric acid secretion was reduced by 71.6% to 99.6% and pepsin secretion was reduced by 29.5% to 96.9%.

<table>
<thead>
<tr>
<th></th>
<th>Reduction in gastric acid secretion (%)</th>
<th>Reduction in pepsin secretion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic secretion</td>
<td>98.0</td>
<td>71.0</td>
</tr>
<tr>
<td>Tetragastrin (4 µg/kg, i.m.) stimulated secretion</td>
<td>94.7</td>
<td>75.1</td>
</tr>
<tr>
<td>Betazole (1 mg/kg, i.m.) stimulated secretion</td>
<td>99.6</td>
<td>96.9</td>
</tr>
<tr>
<td>Insulin (0.2 IU/kg, i.v.) stimulated secretion</td>
<td>71.6</td>
<td>29.5</td>
</tr>
<tr>
<td>Food stimulated secretion</td>
<td>98.9</td>
<td>–</td>
</tr>
</tbody>
</table>

Basic secretion, tetragastrin-stimulated secretion and betazole-stimulated secretion were inhibited after intravenous administration of 20 mg of famotidine.

(2) Nocturnal secretion

Seven hour secretion of gastric acid and pepsin (from 23:00 to 6:00) in healthy adults and in patients with peptic ulcers was reduced by 91.8% and 71.8%, respectively, after oral administration of 20 mg of famotidine.

(3) 24 hr secretion/gastric pH

Gastric secretion in healthy adults was inhibited for 12 hr or greater (from 20:00) by oral administration of 20 mg of famotidine, and the reduction in gastric acid secretion was 93.8%. The gastric pH was 4 or greater at 1 hr after administration, and ranged from 5 to 6 during the 12 hr period.

(4) Blood concentration and the inhibitory effect on gastric acid secretion

Positive correlations were observed between blood concentrations of famotidine and its inhibitory effect on gastric acid secretion. The blood concentration which inhibited gastric acid secretion by 50% was 13 ng/mL.

(5) Effect on hepatic hemodynamics

Intravenous administration of 20 mg of famotidine had no effect on hepatic blood flow or on portal blood flow in healthy adults.

(6) Effect on blood gastrin levels

No effect on blood gastrin levels was observed in patients with gastric or duodenal ulcers treated with 20 mg twice a day orally for 1 to 2 months.

(7) Effect on blood prolactin, etc.

Intravenous administration of 20 mg of famotidine or oral administration of 20 mg twice a day for 4 weeks showed no effect on blood prolactin, gonadotropic hormone, or sex hormone levels in healthy adults or in patients with peptic ulcers.

2. Effects on animals

(1) Histamine H₂-receptor antagonistic effect

The antagonistic effects of famotidine on histamine H₂-receptors, measured by indices which included the heart rate in an isolated guinea pig's atrium, the contraction of an isolated rat's uterus, and gastric secretion in dogs, were 10 to 148 times stronger than those of cimetidine.

(2) Inhibition of gastric acid secretion

The inhibitory effects of famotidine on gastric acid secretion induced by histamine stimulation in dogs were about 40 times more potent and about 1.3 to 1.5 times longer in duration of action than that of cimetidine.

(3) Effect on gastric mucous secretion

There was significant inhibition of the decrease in glycoprotein in gastric mucosa induced by stress in rats.

(4) Effects on experimental ulcers

Famotidine shows a more potent suppressive effect than cimetidine on gastric ulcers induced by indomethacin, aspirin, prednisolone, stress and pyloric ligation, and on duodenal ulcers induced by cysteamine and mepirizole. Moreover, repeated administration accelerated the healing of gastric ulcers induced by acetic acid, and duodenal ulcers induced by mepirizole, and these effects were stronger than those of cimetidine.

(5) Effects on gastric hemorrhage

Famotidine showed a suppressive effect on gastric hemorrhage induced in rats by exsanguination and histamine administration.

(6) Effect on acute gastric mucosal lesions

Famotidine not only suppressed the development of gastric mucosal lesions induced by taurocholate-histamine, taurocholate-serotonin, hydrochloric acid-aspirin and hydrochloric acid-ethanol, but also accelerated the healing of gastric mucosal lesions induced by iodoacetamide.
3. Mechanism of action
This drug exerts a therapeutic effect on gastric ulcers, duodenal ulcers, gastritis, etc. by suppressing gastric acid secretion by means of blockade of histamine H2-receptors in the parietal cells of the gastric mucosa.

PHYSICOCHEMISTRY

Nonproprietary name:
Famotidine

Chemical name:
N-(1-Amino-3-[[2-(diaminomethyleneamino)-1,3-thiazol-4-yl][methylsulfanyl]propylidene]sulfamide

Molecular formula:
C₈H₁₅N₇O₂S₃

Molecular weight:
337.45

Melting point:
About 164°C (decomposition)

Structural formula:

Description:
Famotidine is a white to yellowish white crystal. It is freely soluble in acetic acid (100), slightly soluble in ethanol (95), very slightly soluble in water. It is soluble in 0.5 mol/L hydrochloric acid test solution. It is gradually colored by light.

PACKAGING

Gaster®D Tablets 10 mg:
Boxes of 100 tablets, 140 tablets, 500 tablets, 560 tablets, and 1,000 tablets in press-through packages
Bottles of 500 tablets

Gaster®D Tablets 20 mg:
Boxes of 100 tablets, 140 tablets, 500 tablets, 560 tablets, and 1,000 tablets in press-through packages
Bottles of 500 tablets

REFERENCES
31) Ikezoe, I. et al.: Reported at the 12th International Congress of Gastroenterology
34) Mori, H. et al.: Reported at the 7th World Congress of Gastroenterology.

REQUEST FOR LITERATURE OR INQUIRY ABOUT PRODUCT SHOULD BE MADE TO:
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