- Proton pump inhibitor -

**Pariet® Tablets 5 mg**

**Pariet® Tablets 10 mg**

<Sodium rabeprazole preparation>

### Caution
Use only as directed by a physician.

### CONTRAINDICATIONS (PARIET is contraindicated in the following patients.)
1. Patients with a history of hypersensitivity to any ingredients of PARIET.
2. Patients on atazanavir sulfate or rilpivirine hydrochloride.

[See “Drug Interactions” section.]

### DESCRIPTION

#### 1. Composition

5 mg tablets: Each single, light yellow, film-coated tablet (enteric coated tablet) contains 5 mg of rabeprazole sodium.

10 mg tablets: Each single, light yellow, film-coated tablet (enteric coated tablet) contains 10 mg of rabeprazole sodium.

They also contain ethylcellulose, yellow ferric oxide, carnauba wax, carmellose calcium, glycerol esters of fatty acid, titanium oxide, magnesium oxide, magnesium stearate, talc, low substituted hydroxypropylcellulose, hydroxypropylcellulose, hypromellose phthalate and D-mannitol as inactive ingredients.

#### 2. Product description

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Dosage form and identification code</th>
<th>Appearance</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARIET Tablets 5 mg</td>
<td>Film-coated tablets (Enteric-Coated tablets)</td>
<td>Face Reverse Lateral</td>
<td>Light yellow</td>
</tr>
<tr>
<td></td>
<td>Diameter (mm) 5.4</td>
<td>Weight (mg) 67</td>
<td>Thickness (mm) 2.7</td>
</tr>
</tbody>
</table>

### INDICATIONS

Gastric ulcer, duodenal ulcer, anastomotic ulcer, reflux esophagitis, Zollinger-Ellison syndrome, non-erosive reflux disease and prevention of gastric and duodenal ulcer recurrences associated with low-dose aspirin therapy

Adjunct to *Helicobacter pylori* eradication in the following diseases:

- Gastric ulcer, duodenal ulcer.
- Gastric MALT lymphoma, idiopathic thrombocytopenic purpura, the stomach after endoscopic resection of early stage gastric cancer, and *Helicobacter pylori* gastritis.

**<Precaution>**

1. The administration of PARIET may mask symptoms of gastric cancer. It is therefore necessary to ascertain that the ulcer is not malignant prior to initiating the administration of this product (except as the adjunct to *Helicobacter pylori* eradication in gastric MALT lymphoma and the stomach after endoscopic resection of early stage gastric cancer.)

2. For prevention of gastric and duodenal ulcer recurrences associated with low-dose aspirin therapy

Administer PARIET in patients who are continuously receiving low-dose aspirin to prevent thrombosis or embolism formation, and confirm whether the patient has a history of gastric ulcer or duodenal ulcer before starting administration.
3. As an adjunct to Helicobacter pylori eradication
   (1) The efficacy of Helicobacter pylori eradication in MALT lymphoma in the advanced stage has not been established.
   (2) Helicobacter pylori eradication for idiopathic thrombocytopenic purpura should be conducted for patients who meet the descriptions in the clinical guidelines.
   (3) The suppressive effect on gastric cancer induced by Helicobacter pylori eradication has only been established in the stomach after endoscopic resection of early stage gastric cancer.
   (4) When using PARIET for the treatment of Helicobacter pylori gastritis, make sure that test results are positive for Helicobacter pylori, and that endoscopy shows Helicobacter pylori gastritis.

DOSAGE AND ADMINISTRATION

Gastric ulcer, duodenal ulcer, anastomotic ulcer and Zollinger-Ellison syndrome
The usual adult dose is 10 mg of sodium rabeprazole administered orally once daily. However, the dosage may be increased up to 20 mg orally once daily depending on the severity of symptoms. Normal administration should be restricted to up to 8 weeks for the treatment of gastric ulcer and anastomotic ulcer, and 6 weeks for duodenal ulcer.

Reflux esophagitis
<Treatment>
The usual adult dose is 10 mg of sodium rabeprazole administered orally once daily. However, the dosage may be increased up to 20 mg orally once daily depending on the severity of symptoms. The usual administration should be restricted to up to 8 weeks. Doses of 10 mg or 20 mg twice daily may be administered orally to reflux esophagitis patients for a further 8 weeks when proton pump inhibitor treatment is ineffective. However, a dose of 20 mg twice daily should only be administered to patients with severe mucosa injury.

< Maintenance therapy>
For the maintenance therapy of reflux esophagitis with repeated recurrence and recrudescence, the usual adult dose is 10 mg orally once daily. For the maintenance therapy of reflux esophagitis when proton pump inhibitor treatment is ineffective, dose of 10 mg twice daily may be administered orally.

Non-erosive reflux disease
The usual adult dose is 10 mg of sodium rabeprazole administered orally once daily. The usual administration should be restricted to up to 4 weeks.

Prevention of gastric and duodenal ulcer recurrences associated with low-dose aspirin therapy
The usual dosage for adults is 5 mg as rabeprazole sodium administered orally once daily. The dosage may be increased to 10 mg administered orally once a day in the event of insufficient effect.

Adjunct to Helicobacter pylori eradication
Usually, for adults, the following 3 drugs are taken orally at the same time twice daily for 7 days: 10 mg/dose of sodium rabeprazole, 750 mg (potency)/dose as amoxicillin hydrate, and 200 mg (potency)/dose as clarithromycin. The dose of clarithromycin may be increased as the occasion demands, though the upper limit is 400 mg (potency)/dose twice daily. If Helicobacter pylori eradication with the three-drug regimen of proton pump inhibitor, amoxicillin hydrate and clarithromycin fails, as an alternative treatment, for adults, the following 3 drugs are usually taken orally at the same time twice daily for 7 days: 10 mg/dose of sodium rabeprazole, 750 mg (potency)/dose as amoxicillin hydrate, and 250 mg/dose as metronidazole.

<Precaution>
1. For the treatment of gastric ulcer, duodenal ulcer, anastomotic ulcer and Zollinger-Ellison syndrome, PARIET can be administered at a dose of 20 mg once daily in the case that such conditions are severe, recurrent and intractable.
2. For the treatment of reflux esophagitis, PARIET can be administered at a dose of 20 mg once daily in the case that the condition is severe, recurrent and intractable. (excluding maintenance therapy for reflux esophagitis with repeated recurrence and recrudescence, and cases in which a proton pump inhibitor is ineffective.) The administration of PARIET at 10 mg or 20 mg twice daily for 8 weeks orally in the case of reflux esophagitis for which a proton pump inhibitor is ineffective only applies to patients in whom endoscopic diagnosis shows that reflux esophagitis is not cured. A dose of 20 mg of PARIET twice daily is only applicable to patients with serious mucosa injury. (See ‘CLINICAL STUDIES’ section.)

PRECAUTIONS
1. Careful Administration (PARIET should be administered with care in the following patients.)
   (1) Patients with a history of drug hypersensitivity
   (2) Patients with hepatic function disorder
      (Hepatic encephalopathy has been reported in patients with liver cirrhosis.)
   (3) Elderly patients (See “Use in the Elderly” section.)
2. Important Precautions
   (1) During treatment, the course of the disease should be closely observed and the minimum therapeutic dosing necessary to treat the current condition should be used.
   (2) During the administration of PARIET, it is advisable to observe the patient’s hemogram and liver function carefully, and conduct hematological tests and biochemical tests periodically. If any abnormality is observed, appropriate measures such as discontinuation of the medication should be taken.
   (3) For the treatment of gastric ulcer, duodenal ulcer, anastomotic ulcer and non-erosive reflux disease, it is advisable not to use PARIET for maintenance therapy because there is insufficient experience of long-term use.
   (4) In the maintenance therapy of reflux esophagitis, PARIET can be administered only to patients with repeated recurrence and recrudescence or patients to who proton pump inhibitor is ineffective. Administration to patients who do not need maintenance therapy should be avoided. When lifestyle improvements with respect to...
diet and alcohol consumption have been achieved, and there has been no recurrence over a long period, administration should be discontinued or dose should be reduced. Careful observation by such means as periodic endoscopy is recommended during maintenance therapy.

(5) Treatment for non-erosive reflux disease with PARIET should be applied to patients with repetitive reflux symptoms such as heartburn and acid reflux (about twice times in a week). The administration of PARIET may mask symptoms of malignant tumor such as gastric cancer or esophageal cancer and other digestive diseases. It is therefore necessary to ascertain that above diseases are not present in patients endoscopically prior to initiating the administration of this product.

(6) When PARIET is administered to a patient with non-erosive reflux disease, the physician should confirm the efficacy of treatment about 2 weeks later. If symptoms do not improve, it is possible that they are not caused by reflux. In this case, the physician should undertake another treatment protocol.

(7) When PARIET is used as an adjunct to Helicobacter pylori eradication, it is essential to refer to contraindications, careful administration, clinically significant adverse reactions and other precautions mentioned in the package inserts of other drugs used in the eradication.

3. Drug Interactions
It has been reported that the hepatic enzyme cytochromes P4502C19 (CYP2C19) and 3A4 (CYP3A4) are involved in the metabolism of PARIET. [See “PHARMACOKINETICS” section.]

Gastric acid antisecretory effect of PARIET may promote or inhibit absorption of concomitant drugs.

1) Contraindications for coadministration (PARIET should not be 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>Atazanavir sulfate (REVATAZ)</td>
<td>Effect of atazanavir sulfate may diminish.</td>
<td>Antisecretory effect of PARIET on gastric acid may increase intragastric pH, and reduce solubility of atazanavir sulfate, resulting in a decrease in the blood concentration of atazanavir.</td>
</tr>
<tr>
<td>Rilpivirine hydrochloride (EDURANT)</td>
<td>Effects of rilpivirine hydrochloride may diminish.</td>
<td>Antisecretory effects of PARIET on gastric acid may increase intragastric pH, and reduce absorption of rilpivirine hydrochloride, resulting in decreased blood concentrations of rilpivirine.</td>
</tr>
</tbody>
</table>

2) Precautions for coadministration (PARIET should be administered with care when coadministered with the following drugs.)

<table>
<thead>
<tr>
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<th>Signs, Symptoms, and Treatment</th>
<th>Mechanism and Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>Blood concentration of digoxin and metildigoxin may increase.</td>
<td>Gastric acid antisecretory effect of PARIET may increase intragastric pH, resulting in promote absorption of digoxin and metildigoxin.</td>
</tr>
</tbody>
</table>

4. Adverse Reactions

Gastric ulcer, duodenal ulcer, anastomotic ulcer, reflux esophagitis, Zollinger-Ellison syndrome and non-erosive reflux disease

In clinical trials conducted up to the time of marketing approval, adverse reactions (including laboratory abnormalities) were reported in 277 of 2,509 patients (11.0%). Major adverse reactions were as follows: elevation of ALT (GPT) in 29 patients (1.2%), elevation of AST (GOT) in 21 patients (0.8%).

In the post-marketing surveillance/study, adverse reactions (including laboratory abnormalities) were reported in 299 of 7,020 patients (4.3%). Major adverse reactions were as follows: diarrhea in 19 patients (0.3%), elevation of Al-P in 19 patients (0.3%), constipation in 16 patients (0.2%). (At the time of reexamination period)

Prevention of gastric and duodenal ulcer recurrences associated with low-dose aspirin therapy

In clinical trials conducted up to the time of marketing approval, adverse reactions (including abnormal laboratory test values) have been reported in 44 patients (10.9%) out of a total of 405. Major adverse reactions were diarrhea in 6 patients (1.5%) and constipation in 5 patients (1.2%).

Adjunct to Helicobacter pylori eradication in gastric ulcer or duodenal ulcer

In clinical trials conducted up to the time of marketing approval (three-drug regimen of sodium rabeprazole, amoxicillin hydrate and clarithromycin), adverse reactions were reported in 205 of 508 patients (40.35%). Major adverse reactions were as follows: diarrhea in 93 patients (18.3%); rash in 52 patients (10.2%); and dysgeusia in 25 patients (4.9%).

In the post-marketing surveillance (three-drug regimen of sodium rabeprazole, amoxicillin hydrate and clarithromycin), adverse reactions were reported in 166 of 3,789 patients (4.38%). Major adverse reactions were as follows: diarrhea in 66 patients (1.7%); rash in 22 patients (0.6%); and dysgeusia in 20 patients (0.5%) (at the time of reexamination period).

However, no clinical trial has been conducted to determine the incidence of adverse reactions, in the three-drug regimen of sodium rabeprazole, amoxicillin hydrate and metronidazole in Japan. (At the time of approval)
Adjunct to *Helicobacter pylori* eradication in gastric MALT lymphoma, idiopathic thrombocytopenic purpura, the stomach after endoscopic resection of early stage gastric cancer, and *Helicobacter pylori* gastritis. There has been no clinical trial on the incidence of adverse reactions in the three-drug regimen of sodium rabeprazole, amoxicillin hydrate and clarithromycin/metronidazole in Japan. (At the time of approval)

(1) Clinically significant adverse reactions

1) Shock and anaphylaxis

Shock (incidence unknown) or anaphylaxis (incidence unknown) may occur. Patients should be carefully observed, and if such abnormalities are observed, treatment should be discontinued and appropriate measures taken.

2) Pancytopenia, agranulocytosis, thrombocytopenia and hemolytic anemia

Pancytopenia (incidence unknown), agranulocytosis (incidence unknown), thrombocytopenia (incidence unknown), and hemolytic anemia (incidence unknown) may occur. Patients should be carefully observed, and if such abnormalities are observed, treatment should be discontinued and appropriate measures taken.

3) Fulminant hepatitis, hepatic function disorders and jaundice

Fulminant hepatitis (incidence unknown), hepatic function disorders (5%\( \geq \) 0.1%) and jaundice (incidence unknown) may occur. Patients should be carefully observed, and if such abnormalities are observed, treatment should be discontinued and appropriate measures taken.

4) Interstitial pneumonia

Interstitial pneumonia (incidence unknown) may occur. If symptoms such as fever, coughing, dyspnea and abnormal lung sounds (crepitations) occur, thoracic radiography or other examination should be performed immediately. Administration should be discontinued, and appropriate measures should be taken, such as treatment with cortical steroid hormones.

5) Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme

Dermatopathies such as toxic epidermal necrolysis (TEN) (incidence unknown), oculomucocutaneous syndrome (Stevens-Johnson syndrome) (incidence unknown) and erythema multiforme (incidence unknown) may occur. Patients should be carefully observed, and if such abnormalities are observed, treatment should be discontinued and appropriate measures taken.

6) Acute kidney injury, interstitial nephritis

Acute kidney injury (incidence unknown) and interstitial nephritis (incidence unknown) may occur. Caution should be exercised with respect to renal function tests (BUN, creatinine, etc.) If any such abnormalities are observed, treatment should be discontinued and appropriate measures taken.

7) Hyponatremia

Hyponatremia (incidence unknown) may occur. If any such abnormality is observed, treatment should be discontinued and appropriate measures taken.

8) Rhabdomyolysis

Rhabdomyolysis (incidence unknown) characterized by myalgia, weakness, increased CK (CPK) and increased myoglobin in blood or urine may occur. If such symptoms occur, appropriate measures, such as immediate discontinuation of this product, should be taken.

(2) Clinically significant adverse reaction (analogous compounds)

With analogous compounds (omeprazole), the following adverse reactions have been reported:

1) Visual disturbance

Visual disturbance may occur. If any such abnormality is observed, treatment should be discontinued and appropriate measures taken.

2) Confusion

Delirium, abnormal behavior, disorientation, hallucination, anxiety, irritation, aggressiveness, etc. may occur. In the case of such symptoms, treatment should be discontinued and appropriate measures taken.

(3) Other adverse reactions

Gastric ulcer, duodenal ulcer, anastomotic ulcer, reflux esophagitis, Zollinger-Ellison syndrome, non-erosive reflux disease and prevention of gastric and duodenal ulcer recurrences associated with low-dose aspirin therapy

In the case of the adverse reactions below, appropriate treatment should be started according to the patient’s symptoms.

<table>
<thead>
<tr>
<th>Hypersensitivity</th>
<th>Hematologic</th>
<th>Hepatic</th>
<th>Cardiovascular</th>
<th>Gastrointestinal</th>
<th>Psychoneurologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% &gt; ≥0.1%</td>
<td>&lt;0.1%</td>
<td>Incidence unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash and itching</td>
<td>Leukopenia, leukocytosis, eosinophilia and anemia</td>
<td>Elevation of AST (GOT), ALT (GPT), AL-P, γ-GTP and LDH</td>
<td>Increase in blood pressure</td>
<td>Constipation, diarrhea, feeling of enlarged abdomen, nausea and stomatitis</td>
<td>Headache</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Erythocytopenia, neutrophilia and lymphopenia</td>
<td>Elevation of total bilirubin</td>
<td>Palpitations</td>
<td>Abdominal pain, bitter taste, canculosis, heavy feeling of stomach, thirst, anorexia and fluence</td>
<td>Dizziness, light headed, sleepiness, weakness in the extremities, hypoesthesia, decreased grip strength, impaired tongue movement and disorientation</td>
</tr>
</tbody>
</table>

Hyponatremia (incidence unknown) may occur. If any such abnormality is observed, treatment should be discontinued and appropriate measures taken.
5. Use in the Elderly

PARIET is metabolized mainly in the liver. Since the elderly often have reduced physiological function, they may be at an increased risk of adverse reactions. When adverse reactions such as gastrointestinal symptoms (see “Adverse Reactions” section) occur, careful administrations including the withdrawal of PARIET are required for these patients.

6. Use during Pregnancy, Delivery or Lactation

(1) PARIET should only be used in pregnant women or women suspected of being pregnant if the expected therapeutic benefits outweigh the possible risks associated with treatment.

Fetotoxicity (delayed ossification in rats, weight loss and delayed ossification in rabbits) has been reported with PARIET in animal studies (400 mg/kg p.o. in rats, 30 mg/kg i.v. in rabbits). Also, in an animal study in which sodium rabeprazole (25 mg/kg/day), amoxicillin hydrate (≥400 mg/kg/day) and clarithromycin (≥50 mg/kg/day) were concomitantly given to rats for 4 weeks, aggravation of nutritional state was observed in females.

(2) It is advisable to avoid administration to nursing mothers. If the administration is considered necessary, breast feeding should be interrupted.

[In an animal study (in rats), it has been reported that PARIET is excreted in breast milk.]

7. Pediatric Use

The safety of PARIET in children has not been established (no clinical experience).

8. Precautions concerning Use

(1) Administration

Since PARIET is an enteric coated tablet, patients should be instructed not to chew or crush the tablet, but swallow it whole.

(2) Caution in handing over drug

For drugs that are dispensed in a press-through package (PTP), patients should be instructed to remove the drugs from the package prior to use. [Swallowing the PTP sheet by mistake has been reported to cause puncture in the esophageal mucosa due to sharp corners of the sheet, resulting in perforation and in serious complications such as mediastinitis.]

9. Other Precautions

(1) It has been reported that in a toxicity study in which 5 mg/kg/day or greater of sodium rabeprazole was administered orally to rats for 2 years, carcinoids were observed in the stomachs of female rats.

(2) Increases in thyroid weight and blood thyroxine levels have been reported in animal studies (rats, oral administration of 25 mg/kg/day or greater). Therefore, thyroid function should be carefully monitored during the administration of PARIET.

(3) Benign gastric polyp has been reported during long-term administration of PARIET.

(4) Several foreign observational studies suggest that proton pump inhibitor therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose and long-term (a year or longer) therapy.

(5) In several overseas observational studies conducted mainly in inpatients, increased risk of gastrointestinal infection due to *Clostridium difficile* has been reported in patients treated with proton pump inhibitors.

(6) Caution on the ¹³C-urea breath test: ¹³C-urea breath test may show false negative results during and immediately after administration of proton pump inhibitors, such as sodium rabeprazole, antibiotics, such as amoxicillin hydrate and clarithromycin, and metronidazole. It is, therefore, advisable to perform the ¹³C-urea breath test to determine the result of Helicobacter pylori eradication at a
pharmacokinetics

1. Blood concentrations

(1) Single oral administration of sodium rabeprazole

The changes over time in the mean plasma sodium rabeprazole concentration when administered orally to healthy adult male volunteers at a dose of 20 mg during fasting or after a meal are shown in the figure below. Mean values of pharmacokinetic parameters determined for individual subjects during fasting and postprandial administration of PARIET are presented in the table below. \( t_{\text{max}} \) was prolonged by 1.7 hr after postprandial administration compared to administration during fasting, and inter-individual variations in absorption were observed. 1

2. Concomitant administration of 3 drugs

The following table shows the mean values of pharmacokinetic parameters when sodium rabeprazole 20 mg \( \text{EM}^{*} \), amoxicillin hydrate 750 mg (potency) and clarithromycin 400 mg (potency) were repeatedly administered orally to healthy adult male volunteers twice daily for 7 days (total of 12 times).

Note) Approved dosage and administration details are as follows. Usually, for adults, the following 3 drugs are orally administered at the same time twice daily for 7 days: 10 mg/dose of sodium rabeprazole, 750 mg (potency)/dose as amoxicillin, and 200 mg (potency) dose as clarithromycin. The dose of clarithromycin may be increased as the occasion demands, though the upper limit is 400 mg (potency)/dose twice daily.

2. Metabolism

When PARIET was administered orally to healthy adult male volunteers at single doses of 10 mg and 20 mg, the main metabolite recognized in plasma was its thioether mercapturate conjugated-form. 3

3. Urinary excretion

No unchanged drug was detected in the urine of healthy adult male volunteers up to 24 hr after oral administration of 20 mg of sodium rabeprazole, and about 29-40% of the dose was excreted in the urine as the carboxylic acid form and its glucuronide, and about 13-19% of the dose was present as the mercapturate conjugated-form. 3

4. Drug interaction

It has been reported that PARIET had no effect on blood concentrations of diazepam and warfarin (R-warfarin) though
The following table shows endoscopic cure rates after an 8-week patients with H2-receptor antagonist resistant reflux esophagitis 10 mg once a day over 24 weeks in the maintenance therapy for Ellison syndrome was 100%.6-14)

Note2) Uncured cases after more than 8 weeks treatment with 10 mg or

a) 10 mg twice daily group

Note1) Uncured cases after more than 8 weeks treatment with

b) Based on the log-rank test

c) Estimated using the Kaplan-Meier method

2. Non erosive gastroesophageal reflux disease

In a double-blind clinical trial (dosing period: 4 weeks) of PARIET administered at 10 mg once a day in patients with non-erosive gastroesophageal reflux disease, the complete disappearance rate and remission rate for the heartburn symptom were 43.6% (44/101 patients) and 55.4% (56/101 patients) respectively. 17)

3. Prevention of gastric and duodenal ulcer recurrences associated with low-dose aspirin therapy

The table below shows cumulative rates of recurrence for gastric and duodenal ulcer at 24 weeks after administration estimated using the Kaplan-Meier method in a double-blind comparative study involving patients requiring long-term treatment with low-dose aspirin (at 61 mg or 100 mg/day) with a past history of gastric ulcer or duodenal ulcer 18).

The results of open-labeled and double-blind clinical trials (dosing period: 6-8weeks) conducted with PARIET administered at 10 or 20 mg once a day in patients with gastric ulcer, duodenal ulcer, reflux esophagitis and anastomotic ulcer are summarized in the following table.

The overall improvement rate in 2 patients with Zollinger-Ellison syndrome was 100%.6-14)

The endoscopic non-recurrence rate of PARIET administered at 10 mg once a day in patients with reflux esophagitis resistive to treatment 15) with standard doses of proton pump inhibitors.

Note1) Uncured cases after more than 8 weeks treatment with 10 mg or

20 mg of omeprazole daily or 20 mg of esomeprazole daily, and recurrent cases during maintenance therapy.

The following table shows endoscopic cure rates after an 8-week dosing period with PARIET for patients with reflux esophagitis resistive to treatment with standard doses of proton pump inhibitors 15).

The following table shows endoscopic cure rates after an 8-week treatment with PARIET for patients with reflux esophagitis resistive to treatment 16) with standard doses of proton pump inhibitors 16).

The table below shows cumulative rates of recurrence for gastric ulcer or duodenal ulcer based on Kaplan-Meier method 16).

Furthermore, cumulative rates of recurrence for gastric or duodenal ulcer estimated using the Kaplan-Meier method in patients who continued to receive PARIET beyond 24 weeks up to 52 weeks (up to 76 weeks in total) were 3.7% (95% confidence interval, 0.72%, 6.75%) at 10 mg once a day and 2.2% (95% confidence interval, 0.35, 5.51) at 5 mg once a day. After 24 weeks of treatment, patients in the control group were started on PARIET in place of the control drug at 5 or 10 mg once a day and continued taking the drug for up to 52 weeks.

### CLINICAL STUDIES

1. Gastric ulcer, duodenal ulcer, anastomotic ulcer, reflux esophagitis and Zollinger-Ellison syndrome

The results of open-labeled and double-blind clinical trials (dosing period: 6-8weeks) conducted with PARIET administered at 10 or 20 mg once a day in patients with gastric ulcer, duodenal ulcer, reflux esophagitis and anastomotic ulcer are summarized in the following table.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Endoscopic healing rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric ulcer</td>
<td>95.2% (401/421)</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>98.1% (364/371)</td>
</tr>
<tr>
<td>Reflux esophagitis</td>
<td>90.9% (50/55)</td>
</tr>
<tr>
<td>Anastomotic ulcer</td>
<td>83.3% (10/12)</td>
</tr>
</tbody>
</table>

The overall improvement rate in 2 patients with Zollinger-Ellison syndrome was 100%.6-14)

The endoscopic non-recurrence rate of PARIET administered at 10 mg once a day over 24 weeks in the maintenance therapy for patients with H2-receptor antagonist resistant reflux esophagitis in a double blind clinical trial was 78.6 % (33/42).

The following table shows endoscopic cure rates after an 8-week dosing period with PARIET for patients with reflux esophagitis resistive to treatment with standard doses of proton pump inhibitors 15).

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The overall improvement rate in 2 patients with Zollinger-Ellison syndrome was 100%.6-14)
4. Adjunct to Helicobacter pylori eradication in gastric ulcer or duodenal ulcer

The following table shows eradication rates in a clinical trial conducted in Japan for patients with Helicobacter pylori-positive gastric ulcer or duodenal ulcer (oral administration at the same time twice daily for 7 days of sodium rabeprazole, amoxicillin hydrate and clarithromycin) [19].

<table>
<thead>
<tr>
<th>Dose of each drugs</th>
<th>Frequency of administration</th>
<th>Eradication rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Gastric ulcer</td>
</tr>
<tr>
<td>Sodium rabeprazole 10 mg</td>
<td>Twice/day</td>
<td>87.7% (57/65 patients)</td>
</tr>
<tr>
<td>Amoxicillin hydrate 750 mg (potency)</td>
<td>Twice/day</td>
<td>89.5% (61/68 patients)</td>
</tr>
<tr>
<td>Clarithromycin 200 mg (potency)</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Twice/day</td>
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<td>Twice/day</td>
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</tr>
<tr>
<td>Clarithromycin 400 mg (potency)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Similar results were obtained in a clinical trial conducted outside Japan on eradication in Helicobacter pylori-positive gastric ulcer and duodenal ulcer patients.

Note) The dosage regimen was different from the approved dosage and administration in Japan. (See DOSAGE AND ADMINISTRATION.) The dosages and duration of administration for the 3 drugs were as shown below.

Twice daily for 7 days: 20 mg/dose of sodium rabeprazole, 1000 mg (potency)/dose as amoxicillin hydrate, and 500 mg (potency)/dose as clarithromycin.

In addition, it has been reported that the eradication rate was 82% (49/60 patients) in a clinical trial conducted in Japan with oral administration of sodium rabeprazole, amoxicillin hydrate and metronidazole of the same time twice daily for 7 days in patients with Helicobacter pylori-positive gastric ulcer or duodenal ulcer who had failed the eradication in the three-drug regimen of proton pump inhibitor (lansoprazole), amoxicillin hydrate and clarithromycin [20].

PHARMACOLOGY

1. Mechanism of action

PARIET is transformed to the active form (sulfenamide form) at parietal cells in acidic conditions, and acts by modification of SH-groups of the proton pump (H+, K+-ATPase) causing inhibition of enzyme activity resulting suppression of acid secretion. It is believed that the recovery of enzyme activity is mainly due to drug elimination from the active site, or that glutathione may be involved in the elimination of the active drug. The involvement of glutathione in recovery of enzyme activity is also suspected.

2. Action in humans

(1) Inhibition of gastric acid secretion

When PARIET was administered to healthy adult male volunteers at 10 mg or 20 mg once a day, gastrin-stimulated acid output was significantly decreased from the 1st day of administration. The mean percentages of acid output reduction compared with the day before first dose on day 1 and on day 7 were, at 10 mg once a day, 73 % and 80%, and at 20 mg once a day, 88-89% and 99%, respectively [21, 22].

(2) Increase reaction of intragastric pH

Administration of PARIET at 5, 10 and 20 mg once a day all resulted in a significantly increased intragastric pH in healthy adult men. The proportion of time that showed a pH of 4 or above in the period of 24 hours on day 5 of administration was 46% and 63% for EM’ and PM’ at 5 mg once a day, respectively, 58% and 72% for EM’ and PM’ at 10 mg once a day, respectively, and 61% and 76% for EM’ and PM’ at 20 mg once a day, respectively. 2)

* See Section 1. (1) under the PHARMACOKINETICS section.

3. Action in animals

(1) Inhibition of H+, K+-ATPase (in vitro)

Sodium rabeprazole strongly inhibits H+, K+-ATPase in preparations made from pig gastric mucosa. [23, 24]

(2) Inhibition of gastric acid secretion

1) Sodium rabeprazole inhibits gastric acid secretion stimulated by dibutyl cyclic-AMP in isolated rabbit gastric glands (in vitro). [25]

2) Sodium rabeprazole exhibits strong inhibition of gastric acid secretion stimulated by histamine or pentagastrin in chronic gastric fistula dogs as well as basal gastric acid secretion and histamine-stimulated gastric acid secretion in rats. [25, 26, 27]

Compared to other proton pump inhibitors, the reversal of the antisecretory effect is more rapid with sodium rabeprazole and the increase in blood gastrin levels is less in dogs and rats. [25, 28]

(3) Antulcer action

In rats, sodium rabeprazole demonstrated a strong antiulcer action against various experimental ulcers and therapeutic activity in experimental gastric mucosal lesions (induced by cold restraint stress, water immersion stress, pyloric ligation, cyssteamine, ethanol-hydrochloride or aspirin). [26, 29, 30]

4. Adjunctive effect on eradication of Helicobacter pylori

(1) Eradicative effect in Helicobacter pylori-infected animal model

In a Helicobacter pylori-infected animal model using sand rats the concomitant effect of amoxicillin hydrate and clarithromycin on the bacterial count in stomach was enhanced by adding sodium rabeprazole.

(2) Mechanism of adjunctive effect on eradication of Helicobacter pylori

In triple-drug therapy with amoxicillin hydrate and clarithromycin, or with amoxicillin hydrate and metronidazole, the increase in intragastric pH brought about by sodium rabeprazole is considered to enhance the antibacterial activity of amoxicillin hydrate and clarithromycin.

PHYSICOCHEMISTRY

Nonproprietary name: Rabeprazole Sodium (JAN)

Chemical name:

- Monosodium(RS)-2-[(4-(3-methoxypropoxy)-3-methylpyridin-2-yl)methyl]sulfinyl]-1H-benzimidazolide

Molecular formula: C_{13}H_{20}N_{3}NaO_{7}

Molecular weight: 381.42
**Eisai Co., Ltd.**

**Structural formula:**

![Structural formula of Rabeprazole sodium](image)

**Description:**

Rabeprazole sodium occurs as a white to pale yellowish white powder. It is very soluble in water, freely soluble in ethanol (99.5).

It dissolves in 0.01 mol/L sodium hydroxide solution. It is hygroscopic.

A solution of Rabeprazole sodium (1 in 20) shows no optical rotation.

Rabeprazole sodium shows crystal polymorphism.

Melting point: 225°C (with decomposition)

**Partition coefficient:** about 214 (pH7.0, water: octanol)

**APPROVAL CONDITIONS**

Formulate a risk management plan for drugs, and implement the plan appropriately.

**PACKAGING**

**PARIET Tablets 5 mg:**
- Boxes of 100, 140 (14Tabs.×10) in press-through packages, and bottles of 100

**PARIET Tablets 10 mg:**
- Boxes of 100, 140 (14Tabs.×10), 280 (14Tabs.×20), 500 and 700 (14Tabs.×50) in press-through packages, and bottles of 100

**REFERENCES**

30) Data on file: Effect of Rabeprazole Sodium on Aspirin induced Gastric Mucosal Lesion in Rats (2012)

**REQUESTS FOR LITERATURE AND PRODUCT INFORMATION SHOULD BE MADE TO:**

Customer Drug Information Service

Free Dial: 0120-917-719

EA Pharma Co., Ltd.

1-1, Irifune 2-chome, Chuo-ku, Tokyo, 104-0042

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**Marketed by:**

EA Pharma Co., Ltd.

1-1, Irifune2-chome, Chuo-ku, Tokyo, 104-0042

**BRAND NAMES IN OTHER COUNTRIES**

Aciphex (U.S.A.)

Parit (India)