

Revised: April 2012 (21st version)

Standard Commodity Classification No. of Japan
872329

- Proton pump inhibitor -

Pariet® Tablets 20 mg

<Sodium rabeprazole preparation>

Prescription drug

Storage	Approval No.	20900AMZ00602000
PARIET should be stored at room temperature. PARIET should be protected from moisture after opening aluminum bag. (The content may be reduced by moisture.)	Date of listing in the NHI reimbursement price	Dec 1997
	Date of initial marketing in Japan	Dec 1997
	Date of latest reexamination	Feb 2008
	International birth date	Oct 1997
Expiration date		
PARIET should be used before the expiration date indicated on the package or label (It is also recommended that PARIET be used as soon as possible after opening package.).		

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. [See "Drug Interactions" section.]

DESCRIPTION**1. Composition**

Each light yellow, film-coated tablet (enteric coated tablet) contains 20 mg of sodium rabeprazole.

It also contains ethylcellulose, yellow ferric oxide, carnauba wax, 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

Brand name	Dosage form and identification code	Appearance			Description
		Face	Reverse	Lateral	
PARIET Tablets 20 mg	Film-coated tablets (Enteric-coated tablets)				Light yellow
	●ノゾエツト20	Diameter (mm) 7.2	Weight (mg) 163	Thickness (mm) 3.6	

INDICATIONS

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

<Precaution>

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.

DOSAGE AND ADMINISTRATION**Gastric ulcer, duodenal ulcer, anastomotic ulcer and Zollinger-Ellison syndrome**

The usual adult dose for oral use is 10 mg of sodium rabeprazole administered 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 for the treatment of gastric ulcer and anastomotic ulcer, and 6 weeks for duodenal ulcer.

Reflux esophagitis

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.

<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 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 and anastomotic ulcer, it is advisable not to use PARIET for maintenance therapy because there has not been sufficient experience in long-term use.

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.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Atazanavir sulfate (REYATAZ)	Effect of atazanavir sulfate may diminish.	Gastric acid antisecretory effect of PARIET may increase intragastric pH, and reduce solubility of atazanavir sulfate, resulting in a decrease in the blood concentration of atazanavir sulfate.

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

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Digoxin Metildigoxin	Blood concentration of digoxin and metildigoxin may increase.	Gastric acid antisecretory effect of PARIET may increase intragastric pH, resulting in promote absorption of digoxin and metildigoxin.
Itraconazole Gefitinib	Blood concentration of itraconazole and gefitinib may decrease.	Gastric acid antisecretory effect of PARIET may increase intragastric pH, resulting in inhibit absorption of itraconazole and gefitinib.

Antacid containing aluminum hydroxide gel/ magnesium hydroxide	It has been reported that the mean area under the plasma sodium rabeprazole concentration-time curve (AUC) decreases by 8 and 6% after concomitant administration of PARIET and antacid, and administration of PARIET at 1 hr after the antacid, respectively, compared to the administration of PARIET alone.
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4. Adverse Reactions

In clinical trials, adverse reactions (including laboratory abnormalities) were reported in 241 of 1,992 patients (12.1%). Major adverse reactions were as follows: elevation of ALT (GPT) in 29 patients (1.5%), elevation of AST (GOT) in 21 patients (1.1%), elevation of LDH in 18 patients (0.9%). (At the time of approval. Above numbers of cases include cases from two clinical trials: maintenance therapy with PARIET 10 mg for reflux esophagitis showing repeated recurrence and recrudescence, and treatment with PARIET 10 mg for non-erosive reflux disease.)

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 AI-P in 19 patients (0.3%), constipation in 16 patients (0.2%). (At the time of reexamination period. Above numbers of cases include cases from the post-marketing surveillance/study conducted in the reexamination period for maintenance therapy with PARIET 10 mg for reflux esophagitis showing repeated recurrence and recrudescence.)

(1) Clinically significant adverse reactions

1) Shock and anaphylactoid reactions

Shock (incidence unknown) or anaphylactoid reactions (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 (5% > ≥ 0.1%) 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% > ≥ 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 (<0.1%) may occur. If symptoms such as fever, coughing, dyspnoea 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 renal failure, interstitial nephritis

Acute renal failure (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 and lansoprazole), 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) Angioedema, bronchial spasm

Angioedema and bronchial spasm may occur. In the case of such symptoms treatment should be discontinued and appropriate measures taken.

3) 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

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

	5% > ≥0.1%	<0.1%	Incidence unknown
Hypersensitivity	Rash and itching	Urticaria	
Hematologic	Leukopenia, leukocytosis, eosinophilia and anemia	Erythrocytopenia, neutrophilia and lymphopenia	

	5% > ≥0.1%	<0.1%	Incidence unknown
Hepatic	Elevation of AST (GOT), ALT (GPT), ALP, γ -GTP and LDH	Elevation of total bilirubin	
Cardiovascular		Increase in blood pressure and palpitations	
Gastrointestinal	Constipation, diarrhea, feeling of enlarged abdomen and nausea	Abdominal pain, bitter taste, stomatitis, candidiasis, heavy feeling of stomach, thirst, anorexia and flatulence	glossitis and vomiting
Psychoneurologic	Headache	Dizziness, light headed, sleepiness, weakness in the extremities, hypoaesthesia, decreased grip strength, impaired tongue movement and disorientation	Delirium and coma
Others	Elevation of total cholesterol, triglycerides and BUN, and proteinuria, and increase in blood TSH	Edema, malaise, fever, alopecia, numbness and elevation of CK (CPK)	Blurred vision, shifting vision, arthralgia, myalgia, hyperammonemia and gynecomastia

The incidences in the above table are based on the results of clinical trials and post-marketing surveillances.

5. Use in the Elderly

PARIET is metabolized mainly in the liver. Since the physiological functions of the liver are often reduced in the elderly, they are more likely to experience adverse reactions. Therefore, if adverse reactions such as gastrointestinal symptoms (see "Adverse Reactions" section) occur, it is advisable to take measures such as instituting a drug-free interval with careful supervision.

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 (400mg/kg p.o. in rats, 30mg/kg i.v. in rabbits).]

(2) It is advisable to avoid administration to nursing mothers. When PARIET must be used, breast feeding should be discontinued during treatment.

[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), instruct the patient to remove the drug from the package prior to use. [It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, causing perforation and resulting in serious complications such as mediastinitis.]

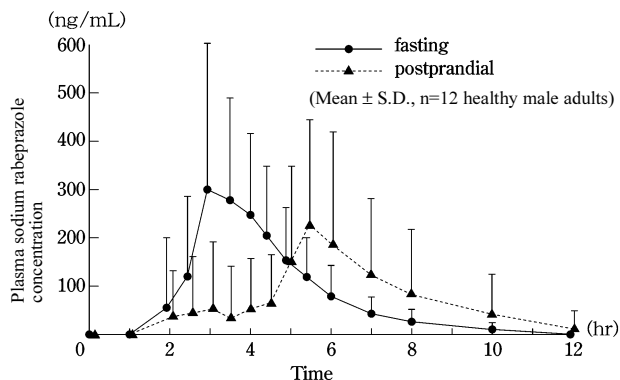
9. Other Precautions

- (1) It has been reported that in a carcinogenicity 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 published 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.

PHARMACOKINETICS

1. Blood concentrations

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_{max} was prolonged by 1.7 hr after postprandial administration compared to administration during fasting, and inter-individual variations in absorption were observed.¹⁾



Plasma sodium rabeprazole concentration after oral administration of PARIET 20 mg during fasting or after a meal

Effect of food on pharmacokinetic parameters

Dose	C_{max} (ng/mL)	t_{max} (hr)	AUC (ng·hr/mL)	$t_{1/2}$ (hr)
Fasting	437 ± 237	3.6 ± 0.9	937 ± 617	1.49 ± 0.68
Postprandial	453 ± 138	5.3 ± 1.4	901 ± 544	1.07 ± 0.47

(Mean ± S.D., n=12)

The following table shows the mean values of pharmacokinetic parameters when sodium rabeprazole was administered orally to healthy adult male volunteers at doses of 10 mg and 20 mg during fasting.²⁾

Pharmacokinetic parameters after single oral administration of PARIET to healthy adult male volunteers

Dose	C_{max} (ng/mL)	t_{max} (hr)	AUC (ng·hr/mL)	$t_{1/2}$ (hr)
10 mg	247 ± 24	3.8 ± 0.5	440 ± 24	0.85 ± 0.04
20 mg	406 ± 64	3.1 ± 0.2	809 ± 186	1.02 ± 0.16

(Mean ± S.E., n=6)

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-form product produced by non-enzymatic reduction reaction. Other metabolites were the demethylated products due to demethylation which involving the hepatic enzymatic metabolism of cytochrome P450C19 (CYP2C19), and the sulfone-form products due to sulfonation involving 3A4 (CYP3A4).^{1, 3, 4)}

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 such effect had been recognized for analogous compound (omeprazole) and attributed to drug interactions involving hepatic enzymatic metabolic competition for cytochrome P450C19 (CYP2C19). It has been reported that PARIET had no effect on blood concentrations of theophylline though such effect had been recognized with analogous compound (lansoprazole) and attributed to induction of hepatic enzymatic metabolism of cytochrome P450A2 (CYP1A2).^{4, 5)}

CLINICAL STUDIES

Clinical efficacy

The results of open-labeled and double-blind clinical trials conducted with PARIET in patients with gastric ulcer, duodenal ulcer, reflux esophagitis and anastomotic ulcer are summarized in the following table.

Disease	Endoscopic healing rate
Gastric ulcer	95.2% (401/421)
Duodenal ulcer	98.1% (364/371)
Reflux esophagitis	90.9% (50/55)
Anastomotic ulcer	83.3% (10/12)

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

The following table shows the 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^{note)}.

	20 mg once daily	10 mg twice daily	20 mg twice daily
total	58.8% (60/102)	78.4% (80/102)	77.0% (77/100)
grade A and grade B*	65.1% (56/86)	87.1% (74/85)	79.5% (66/83)
grade C and grade D*	25.0% (4/16)	35.3% (6/17)	64.7% (11/17)

Note) Uncured cases after more than 8 weeks treatment with 10 mg of sodium rabeprazole daily, 30 mg of lansoprazole daily or 20 mg of omeprazole daily, and recurrent cases during maintenance therapy.

* Severity defined by modified Los Angeles Classification.

It was demonstrated in clinical pharmacology studies that the increase in gastric pH was greater in the 20 mg group than in the 10 mg group, and the usefulness of PARIET in the treatment of intractable ulcer has been demonstrated using a dose of 20 mg once daily.^{7,9)}

PHARMACOLOGY

1. Mechanism of action

PARIET transforms to the activated 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 and consequent acid secretion suppression. 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 compared with the 1st day of administration. The mean percentages of acid output reduction compared with the day before starting administration 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^{15,16)}.

(2) Increase reaction of intragastric pH

When PARIET was administered to healthy adult male volunteers at 10 mg or 20 mg once a day, intragastric pH was significantly increased. The percentage of holding times above pH4 and pH3 in 24 hr on day 4 after treatment with 10 mg was 73 % and 80 % respectively, and for treatment with 20 mg was 78% and 83%, respectively¹⁷⁾.

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.^{18,19)}

(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*).²⁰⁾

2) Sodium rabeprazole exhibits strong inhibition of gastric acid secretion stimulated by histamine or penta-gastrin in chronic gastric fistula dogs as well as basal gastric acid secretion and histamine-stimulated gastric acid secretion in rats.^{20,21,22)}

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.^{20,23)}

(3) Antiulcer 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, cysteamine or ethanol-hydrochloride).^{21,24)}

PHYSICOCHEMISTRY

Nonproprietary name: Rabeprazole Sodium (JAN)

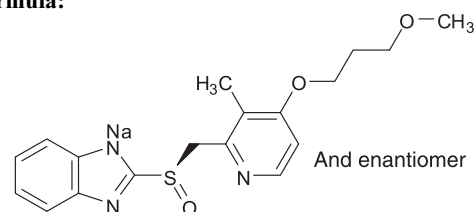
Chemical name:

Monosodium(*RS*)-2-({[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methyl}sulfinyl)-1*H*-benzoimidazolide

Molecular formula: $C_{18}H_{20}N_3NaO_3S$

Molecular weight: 381.42

Structural formula:



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.

It shows no optical rotation.

Melting point: 225°C (with decomposition)

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

PACKAGING

PARIET Tablets 20 mg:

Boxes of 100, 140(14Tabs.×10) and 500 in press-through packages

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Parit (India)