

Principal: Nichi-Iko

Product Name: NIKP-Rabeprazole enteric coated tablet 10mg & 20mg

Version: April 2013

Reference 1: Pariet Tab 10mg (Enteric Coated) (HK-44935) & Pariet Tab 20mg (Enteric Coated)
(HK-44936) HK PI Version: 24 February 2006 (Eisai)

NIKP-Rabeprazole enteric coated tablet 10mg & 20mg Rabeprazole Sodium

Nichi-Iko
Product



This package insert is continually updated: Please read carefully before using a new pack.

1. TRADE NAME OF THE MEDICINAL PRODUCT

NIKP-Rabeprazole enteric coated tablet 10 mg

NIKP-Rabeprazole enteric coated tablet 20 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains:


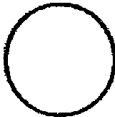

NIKP-Rabeprazole enteric coated tablet 10 mg contains 10mg of rabeprazole sodium, equivalent to 9.42 mg rabeprazole.

NIKP-Rabeprazole enteric coated tablet 20 mg contains 20mg of rabeprazole sodium, equivalent to 18.85 mg rabeprazole.

For full list of Excipients, see section 6.1.

3. PHARMACEUTICAL FORM

- Gastro-resistant tablets
- NIKP-Rabeprazole enteric coated tablet 10mg is a pale yellow film-coated tablet.

Brand name	Appearance			Identification code on tablet
	Weight (mg)	Diameter (mm)	Thickness (mm)	
NIKP-Rabeprazole enteric coated tablet 10mg	 131	 6.8	 3.5	π 892 · 10


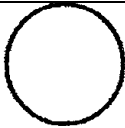
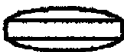
Principal: Nichi-Iko

Product Name: NIKP-Rabeprazole enteric coated tablet 10mg & 20mg

Version: April 2013

Reference 1: Pariet Tab 10mg (Enteric Coated) (HK-44935) & Pariet Tab 20mg (Enteric Coated)
(HK-44936) HK PI Version: 24 February 2006 (Eisai)

- NIKP-Rabeprazole enteric coated tablet 20mg is a pale yellow film-coated tablet.

Brand name	Appearance			Identification code on tablet
	Weight (mg)	Diameter (mm)	Thickness (mm)	
NIKP-Rabeprazole enteric coated tablet 20mg	 150	 7.3	 3.5	π 893-20

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

NIKP-Rabeprazole enteric coated tablets are indicated for the treatment of:

- Duodenal Ulcer
- Gastric Ulcer
- Stomal Ulcer
- Reflux Esophagitis
- Gastro-esophageal reflux disease long-term management (GERD Maintenance)
- Symptomatic treatment of moderate to very severe gastro-esophageal reflux disease (symptomatic GERD)
- Zollinger-Ellison Syndrome
- In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* in patients with peptic ulcer disease. See section 4.2

4.2 Posology and Method of Administration

Adults / elderly:

Duodenal Ulcer, Gastric Ulcer, Stomal Ulcer & Reflux Esophagitis:

The usual adult dose is 10 mg of rabeprazole sodium administered orally once daily. However, the dosage may be increased up to 20 mg orally once a day depending on the severity of symptoms. For the treatment of gastric ulcer, stomal ulcer and reflux esophagitis, the usual administration should be restricted up to 8 weeks, and for duodenal ulcer, 6 weeks.

Principal: Nichi-Iko

Product Name: NIKP-Rabeprazole enteric coated tablet 10mg & 20mg

Version: April 2013

Reference 1: Pariet Tab 10mg (Enteric Coated) (HK-44935) & Pariet Tab 20mg (Enteric Coated)
(HK-44936) HK PI Version: 24 February 2006 (Eisai)

Gastro-Esophageal Reflux Disease Long-term Management (GERD Maintenance):

For long –term management, a maintenance dose of **NIKP-Rabeprazole enteric coated tablet** 10mg or 20mg once daily can be used depending upon patient response.

Symptomatic Treatment of Moderate to Very Severe Gastro-Esophageal Reflux Disease (symptomatic GERD): 10 mg once daily in patients without esophagitis. If symptom control has not been achieved during four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen taking 10 mg once daily when needed.

Zollinger-Ellison Syndrome: The dose varies with the individual patient. A starting dose of 60 mg daily, and doses of up to 100 mg once daily, or 60 mg twice daily have been used. Some patients may require divided doses. Dosing should continue for as long as clinically necessary. Some patients with Zollinger-Ellison Syndrome have been treated continuously for up to one year.

Eradication of H. pylori: Patients with *H. pylori* infection should be treated with eradication therapy. The following combination given for 7 days is recommended:

NIKP-Rabeprazole enteric coated tablet 20 mg twice daily + clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily.

For indications requiring once daily treatment, **NIKP-Rabeprazole enteric coated tablet** should be taken in the morning, before eating; and although neither the time of day nor food intake was shown to have any effect on rabeprazole sodium activity, this regimen will facilitate treatment compliance.

Patients should be cautioned that the **NIKP-Rabeprazole enteric coated tablet** should not be chewed or crushed, but should be swallowed whole.

Renal and hepatic impairment:

No dosage adjustment is necessary for patients with renal or hepatic impairment.

Principal: Nichi-Iko

Product Name: NIKP-Rabeprazole enteric coated tablet 10mg & 20mg

Version: April 2013

Reference 1: Pariet Tab 10mg (Enteric Coated) (HK-44935) & Pariet Tab 20mg (Enteric Coated)
(HK-44936) HK PI Version: 24 February 2006 (Eisai)

See section 4.4 Special Warnings and Precautions for Use of **NIKP-Rabeprazole enteric coated tablet** in the treatment of patients with hepatic impairment.

Children:

NIKP-Rabeprazole enteric coated tablet is not recommended for use in children, as there is no experience of its use in this group.

4.3 Contra-indications

NIKP-Rabeprazole enteric coated tablet is contra-indicated in patients with known hypersensitivity to rabeprazole sodium, substituted benzimidazoles or to any excipient used in the formulation. **NIKP-Rabeprazole enteric coated tablet** is contra-indicated in pregnancy and during breast feeding.

4.4 Special Warnings and Precautions for Use

Symptomatic response to therapy with rabeprazole sodium does not preclude the presence of gastric or esophageal malignancy, therefore the possibility of malignancy should be excluded prior to commencing treatment with **NIKP-Rabeprazole enteric coated tablet**. Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients should be cautioned that **NIKP-Rabeprazole enteric coated tablet** should not be chewed or crushed, but should be swallowed whole.

NIKP-Rabeprazole enteric coated tablet is not recommended for use in children, as there is no experience of its use in this group.

NIKP-Rabeprazole enteric coated tablet in the treatment of patients with hepatic dysfunction the prescriber is advised to exercise caution when treatment with **NIKP-Rabeprazole enteric coated tablet** is first initiated in such patients.

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

Principal: Nichi-Iko

Product Name: NIKP-Rabeprazole enteric coated tablet 10mg & 20mg

Version: April 2013

Reference 1: Pariet Tab 10mg (Enteric Coated) (HK-44935) & Pariet Tab 20mg (Enteric Coated)
(HK-44936) HK PI Version: 24 February 2006 (Eisai)

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

Decreased gastric acidity due to any means, including proton pump inhibitors such as rabeprazole, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter and possibly Clostridium difficile.

4.5 Interaction with other Medicaments and other forms of Interaction

Rabeprazole sodium, as in the case with other members of the proton pump inhibitor (PPI) class of compounds, is metabolized through the cytochrome P450 (CYP450) hepatic drug metabolizing system.

Rabeprazole sodium produces a profound and long lasting inhibition of gastric acid secretion. An interaction with compounds whose absorption is pH dependent may occur.

Co-administration of rabeprazole sodium with ketoconazole may result in a decrease in ketoconazole plasma levels. Co-administration of rabeprazole sodium with digoxin may result in an increase in digoxin plasma levels.

Therefore individual patients may need to be monitored to determine if a dosage adjustment is necessary when such drugs are taken concomitantly with **NIKP-Rabeprazole enteric coated tablet**.

Rabeprazole does not adversely influence plasma concentrations of amoxicillin or clarithromycin when co-administered for the purpose of eradicating upper gastrointestinal *H. pylori* infection.

According to some report, antacids were used concomitantly with the administration of Rabeprazole sodium preparation and no interaction with liquid antacids was observed. There was no clinically relevant interaction with food.

Some report on *in vitro* studies with human liver microsomes indicated that rabeprazole sodium is metabolized by isoenzymes of CYP450 (CYP2C19 and CYP3A4). In this report, at expected human plasma concentrations rabeprazole neither induces nor inhibits CYP3A4; and although *in vitro* studies may not

Principal: Nichi-Iko

Product Name: NIKP-Rabeprazole enteric coated tablet 10mg & 20mg

Version: April 2013

Reference 1: Pariet Tab 10mg (Enteric Coated) (HK-44935) & Pariet Tab 20mg (Enteric Coated) (HK-44936) HK PI Version: 24 February 2006 (Eisai)

always be predictive of *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporin.

Concomitant use of Proton Pump Inhibitors (PPIs) with Methotrexate

Literature suggests that concomitant use of PPIs with Methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. A temporary withdrawal of the PPI may be considered in some patients receiving treatments with high dose methotrexate.

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/ or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted.

4.6 Pregnancy and Lactation

Pregnancy:

There are no data on the safety of rabeprazole in human pregnancy.

Some report on reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus due to rabeprazole sodium, although low fetoplacental transfer occurs in rats. **NIKP-Rabeprazole enteric coated tablet** is contraindicated during pregnancy.

Lactation:

It is not known whether rabeprazole sodium is excreted in human breast milk. No studies in lactating women have been performed. Rabeprazole sodium is however excreted in rat mammary secretions. Therefore **NIKP-Rabeprazole enteric coated tablet** should not be used during breast feeding.

4.7 Effects on ability to Drive and use Machines

Based on the pharmacodynamics properties and the adverse events profile, it is unlikely that **NIKP-Rabeprazole enteric coated tablet** would cause an impairment of driving performance or compromise the ability to use machinery. If however, alertness is impaired due to somnolence, it is recommended that driving and operating complex machinery be avoided.

4.8 Undesirable Effects

Principal: Nichi-Iko

Product Name: NIKP-Rabeprazole enteric coated tablet 10mg & 20mg

Version: April 2013

Reference 1: Pariet Tab 10mg (Enteric Coated) (HK-44935) & Pariet Tab 20mg (Enteric Coated)
(HK-44936) HK PI Version: 24 February 2006 (Eisai)

Based on experience with **NIKP-Rabeprazole enteric coated tablets** and on what is known of other members of proton pump inhibitor, the following undesirable effects must be considered.

The most common adverse events are headache, diarrhoea and nausea. Adverse reactions reported as more than isolated cases are listed below, by system organ class and by frequency.

System Organ Class	Undesirable Effects
Infections and infestations	Infection
Blood and the lymphatic system disorders	Neutropenia, Leucopenia, Thrombocytopenia, Leucocytosis
Immune system disorders	Acute systemic allergic reactions (for example facial swelling, hypotension and dyspnea)*
Metabolism and nutrition disorders	Anorexia
Psychiatric disorders	Insomnia, Nervousness, Somnolence, Depression
Nervous system disorders	Headache, Dizziness
Eye disorders	Visual disturbance
Respiratory, thoracic and mediastinal disorders	Cough, Pharyngitis, Rhinitis, Bronchitis, Sinusitis,
Gastrointestinal disorders	Diarrhoea, Vomiting, Nausea, Abdominal pain, Constipation, Flatulence, Dyspepsia, Dry mouth, Eructation, Gastritis, Stomatitis, Taste disturbance
Hepato-biliary disorders	Hepatitis, Jaundice, Hepatic encephalopathy**
Skin and subcutaneous tissue disorders	Rash, Erythema*, Pruritis, Sweating, Bullous reactions*, Erythema multiforme, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS)
Musculoskeletal connective tissue and bone disorders	Non-specific pain/back pain, Myalgia, Leg cramps, Arthralgia
Renal and urinary disorders	Urinary tract infection, Interstitial nephritis
General disorders and administration site conditions	Asthenia, Flu-like syndrome, Chest pain, Chills, Fever
Investigations	Increased hepatic enzymes**, Weight gain

* Erythema, bullous reactions and acute systemic allergic reactions have usually resolved after discontinuation of therapy.

** Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis. In treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with **NIKP-Rabeprazole enteric coated tablet** is first initiated in such patients (see section 4.4)

4.9 Overdose

Principal: Nichi-Iko

Product Name: NIKP-Rabeprazole enteric coated tablet 10mg & 20mg

Version: April 2013

Reference 1: Pariet Tab 10mg (Enteric Coated) (HK-44935) & Pariet Tab 20mg (Enteric Coated)
(HK-44936) HK PI Version: 24 February 2006 (Eisai)

There is no experience to date with deliberate overdose. Dosages of up to 80 mg/day have been well tolerated. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is, therefore, not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilized.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

ATC code: A02B C04

Mechanism of Action: Rabeprazole sodium belongs to the class of anti-secretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H₂ histamine antagonist properties, but suppress gastric acid secretion by the specific inhibition of the H⁺/K⁺-ATPase enzyme (the acid or proton pump). The effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa. As a weak base, rabeprazole is rapidly absorbed following all doses and is concentrated in the acid environment of the parietal cells. Rabeprazole is converted to the active sulphenamide form through protonation and it subsequently reacts with the available cysteines on the proton pump.

5.2 Pharmacokinetic Properties

Absorption: **NIKP-Rabeprazole enteric coated tablet** is an enteric-coated (gastro-resistant) tablet formulation of rabeprazole sodium. This presentation is necessary because rabeprazole is acid-labile. Absorption of rabeprazole therefore begins only after the tablet leaves the stomach. It is said that absorption is rapid, with peak plasma levels of rabeprazole occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C_{max}) of rabeprazole and AUC are linear over the dose range of 10 mg to 40 mg. Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52% due in large part to pre-systemic metabolism. Additionally the bioavailability does not appear to increase with repeat administration. In healthy subjects the plasma half-life is approximately one hour (range 0.7 to 1.5 hours), and the total body clearance is estimated to be 283±98

Principal: Nichi-Iko

Product Name: NIKP-Rabeprazole enteric coated tablet 10mg & 20mg

Version: April 2013

Reference 1: Pariet Tab 10mg (Enteric Coated) (HK-44935) & Pariet Tab 20mg (Enteric Coated) (HK-44936) HK PI Version: 24 February 2006 (Eisai)

ml/min. Neither food nor the time of day of administration of the treatment affect the absorption of rabeprazole sodium.

Distribution: According to some report, Rabeprazole is approximately 97% bound to human plasma proteins.

Metabolism and excretion: In humans the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl-thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but it is not present in plasma.

It is said that following a single 20 mg ¹⁴C labeled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites; a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites. The remainder of the dose was recovered in feces.

Gender: It is said that adjusted for body mass and height, there are no significant gender differences in pharmacokinetic parameters following a single 20 mg dose of rebeprazole.

Renal dysfunction: According to some report, in patients with stable, end-stage, renal failure requiring maintenance hemodialysis (creatinine clearance $\leq 5\text{ml/min/1.73m}^2$), the disposition of rabeprazole was very similar to that in healthy volunteers. The AUC and the C_{max} in these patients was about 35% lower than the corresponding parameters in healthy volunteers. The mean half-life of rabeprazole was 0.82 hours in healthy volunteers, 0.95 hours in patients during hemodialysis and 3.6 hours post dialysis. The clearance of the drug in patients with renal disease requiring maintenance hemodialysis was approximately twice that in healthy volunteers.

Hepatic dysfunction: It is said that following a single 20 mg dose of rabeprazole to patients with chronic mild to moderate hepatic impairment the AUC doubled and there was a 2-3 fold increase in half-life of rabeprazole compared to the healthy volunteers. However, following a 20 mg dose daily for 7 days the AUC had increased to only 1.5-fold and the C_{max} to only 1.2-fold. The half-life of rabeprazole in patients with hepatic impairment was 12.3 hours compared to 2.1 hours in healthy volunteers. The pharmacodynamic response (gastric pH control) in the two groups was clinically comparable.

Elderly: According to some report, elimination of rabeprazole was somewhat decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium, the AUC approximately doubled, the C_{max} increased by 60%

Principal: Nichi-Iko

Product Name: NIKP-Rabeprazole enteric coated tablet 10mg & 20mg

Version: April 2013

Reference 1: Pariet Tab 10mg (Enteric Coated) (HK-44935) & Pariet Tab 20mg (Enteric Coated)
(HK-44936) HK PI Version: 24 February 2006 (Eisai)

and $t_{1/2}$ increased by approximately 30% as compared to young healthy volunteers. However there was no evidence of rabeprazole accumulation.

CYP2C19 Polymorphism: It is said that following a 20 mg daily dose of rabeprazole for 7 days, CYP2C19 slow metabolizers, had AUC and $t_{1/2}$ which were approximately 1.9 and 1.6 times the corresponding parameters in extensive metabolizers whilst C_{max} had increased by only 40%.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

- NIKP-Rabeprazole enteric coated tablet 10mg
D-mannitol, Microcrystalline Cellulose, Magnesium Oxide, Hydroxypropylcellulose, Carmellose Calcium, Talc, Magnesium Stearate, Hypromellose phthalate, Glycerol Esters of Fatty Acids, Titanium Oxide, Yellow ferric oxide, Carnauba Wax.
- NIKP-Rabeprazole enteric coated tablet 20mg
D-mannitol, Magnesium Oxide, Hydroxypropylcellulose, Carmellose Calcium, Talc, Magnesium Stearate, Ethylcellulose, Hypromellose Phthalate, Glycerol Esters of Fatty Acids, Titanium Oxide, Yellow ferric oxide, Carnauba Wax

6.2 Incompatibilities

None.

6.3 Shelf-Life

3 years before opening aluminum pouch (aluminum pillow –bag.).

6.4 Special Precautions for Storage

Store below 25°C.

Please protect NIKP-Rabeprazole enteric coated tablets from moisture.

Keep out of reach of children.

Do not use after the expiration date indicated on the outer carton.

6.5 Pack size

- NIKP-Rabeprazole enteric coated tablet 10mg
10 (1 x 10's), 30 (3 x 10's), 100 (10 x 10's) tablets.
Not all pack sizes may be marketed.
- NIKP-Rabeprazole enteric coated tablet 20mg

Principal: Nichi-Iko

Product Name: NIKP-Rabeprazole enteric coated tablet 10mg & 20mg

Version: April 2013

Reference 1: Pariet Tab 10mg (Enteric Coated) (HK-44935) & Pariet Tab 20mg (Enteric Coated)
(HK-44936) HK PI Version: 24 February 2006 (Eisai)

10 (1 x 10's), 30 (3 x 10's), 100 (10 x 10's) tablets.

Not all pack sizes may be marketed.

6.6 Instructions for Use/Handling

No specified instruction needed.

7. ADMINISTRATIVE DATA:

7.1 Name of Manufacturer

Nichi-Iko Pharmaceutical Co., Ltd. Toyama Plant 1

205-1, Shimoumezawa Namerikawa-Shi Toyama, 936-0857, Japan

8. DATE OF ISSUE / REVISION:

April 2013

Hong Kong