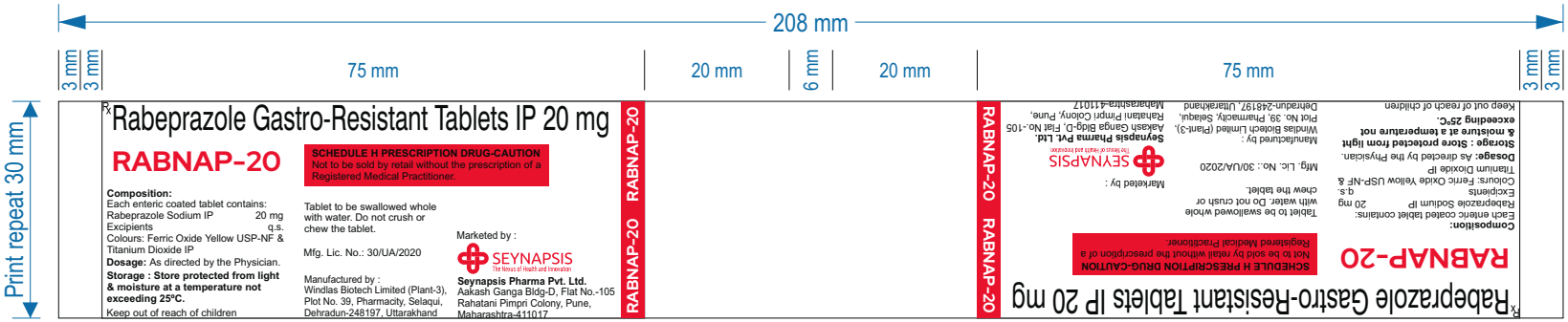
Artwork Details					
Product Name	RABNAP-20	Pack	10x10 Tablets (Sale)	Customer	SEYNAPSIS
Item	Unit Carton	WBPL Item Code		Market	Domestic
Design	Lock bottom top open	Customer Code	NA	Supersedes Item Code	
Layout/Parallel Product	RABIMOND 20	Dimension/Foil Width	105x50x45 mm (ID)	OPZ/NVZ	As per Artwork
Folded/Strip Size	NA	Repeat Length	NA	Grain Direction	Perpendicular to pasting flap
GSM/Foil Thickness	320 GSM	Adhesive/Gum	NA	Barcode/QR Code	NA
Board/Paper/Foil Type	FBB	Release/Liner Paper	NA	Varnish/Coating/Finish	UV
Colour Scheme	CMYK			Change Control No.	
Reason for Change	**NEW ARTWORK**				

Prepared By : PD	Checked By : PD	Checked By: Packing	Checked By: F&D	Checked By: QA	Approved By: QA	Approved by : Customer (if applicable)
Keyline / Design / Colour Scheme / Text Alignment / Dummy Sample	Layout / Dimension / Colour Scheme / Coding Space / Machinability / Item & Artwork Code / Net Content / Specification / Text Matter, Marketing Address	Layout / Dimension / Coding Space / Machinability / Net Content / Specification	Physical parameter of product as per Label Claim (Composition) and change part / Storage Condition	Generic Name & Label Claim (Composition) / Molecule Specific & Statutory Warning / Mfg. Lic. No. / Manufacturing &	–	–
Sign/Date	Sign/Date	Sign/Date	Sign/Date	Sign/Date	Sign/Date	Sign/Date



℞Rabeprazole Gastro-Resistant Tablets IP 20 mg

RABNAP-20

SCHEDULE H PRESCRIPTION DRUG-CAUTION
Not to be sold by retail without the prescription of a Registered Medical Practitioner.

Composition:
Each enteric coated tablet contains:
Rabeprazole Sodium IP 20 mg
Excipients q.s.
Colours: Ferric Oxide Yellow USP-NF & Titanium Dioxide IP
Dosage: As directed by the Physician.
Storage : Store protected from light & moisture at a temperature not exceeding 25ºC.
Keep out of reach of children

Tablet to be swallowed whole with water. Do not crush or chew the tablet.

Mfg. Lic. No.: 30/UA/2020

Manufactured by :
Windlas Biotech Limited (Plant-3), Plot No. 39, Pharmacity, Selaqui, Dehradun-248197, Uttarakhand

Marketed by :
SEYNAPSIS
The Nexus of Health and Innovation
Seynapsis Pharma Pvt. Ltd.
Aakash Ganga Bldg-D, Flat No.-105
Rahatani Pimpri Colony, Pune, Maharashtra-411017

RABNAP-20 RABNAP-20
RABNAP-20 RABNAP-20

Artwork Details

Product Name	RABNAP-20	Pack	10 Tablets (Sale)	Customer	SEYNAPSIS
Item	Foil (Alu-alu Blister)	WBPL Item Code		Market	Domestic
Design	Continuous	Customer Code	NA	Supersedes Item Code	NA
Layout/Parallel Product	Revago-20	Dimension/Foil Width	208 mm	OPZ/NVZ	20 mm
Folded/Strip Size	98 x 41 mm	Repeat Length	30 mm	Grain Direction	NA
GSM/Foil Thickness	0.025 mm (DSO)	Adhesive/Gum	NA	Barcode/QR Code	NA
Board/Paper/Foil Type	Alu Foil+HSL(4-6GSM)	Release/Liner Paper	NA	Varnish/Coating/Finish	NA
Colour Scheme	PANTONE 185 C / BLACK			Change Control No.	NA
Reason for Change	**NEW ARTWORK**				

Prepared By : PD	Checked By : PD	Checked By: Packing	Checked By: F&D	Checked By: QA	Approved By: QA	Approved by : Customer (if applicable)
Keyline / Design / Colour Scheme / Text Alignment / Dummy Sample	Layout / Dimension / Colour Scheme / Coding Space / Machinability / Item & Artwork Code / Net Content / Specification / Text Matter, Marketing Address	Layout / Dimension / Coding Space / Machinability / Net Content / Specification	Physical parameter of product as per Label Claim (Composition) and change part / Storage Condition	Generic Name & Label Claim (Composition) / Molecule Specific & Statutory Warning / Mfg. Lic. No. / Manufacturing &	–	–
Sign/Date	Sign/Date	Sign/Date	Sign/Date	Sign/Date	Sign/Date	Sign/Date

Format No.: QA/CM/063/F/03-01

300 mm

435 mm

PATIENT INFORMATION LEAFLET

For the use of a Registered Medical Practitioner, or a Hospital, or a Laboratory only

Rabeprazole Gastro-Resistant Tablets IP 20 mg

RABNAP-20

1. Generic Name
Rabeprazole Gastro-Resistant Tablets IP 20 mg.

2. Qualitative and quantitative composition
Each enteric coated tablet contains:
Rabeprazole Sodium IP 20 mg
Excipients q.s.
Colours: Ferric Oxide Yellow USP-NF &
Titanium Dioxide IP

3. Dosage form and strength
Oral dosage form (Tablets),
Rabeprazole Sodium 20 mg

4. Clinical particulars
4.1 Therapeutic indication
It is indicated for Gastroesophageal reflux disease, duodenal ulcer & Zollinger Ellison syndrome.

4.2 Posology and method of administration
Table 1 shows the recommended dosage of Rabeprazole Gastro-resistant Tablets in adults and adolescent patients 12 years of age and older. The use of Rabeprazole Gastro-resistant Tablets is not recommended for use in pediatric patients 1 year to less than 12 years of age because the lowest available tablet strength (20 mg) exceeds the recommended dose for these patients. Use another rabeprazole formulation for pediatric patients 1 year to less than 12 years of age.

Table 1: Recommended Dosage and Duration of Rabeprazole Gastro-resistant Tablets in Adults and Adolescents 12 Years of Age and Older

Indication		Dosage of Rabeprazole Gastro-resistant Tablets	Treatment Duration
	Adults		
Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)		20 mg once daily	4 to 8 weeks*
Maintenance of Healing of Erosive or Ulcerative GERD		20 mg once daily	Controlled studies do not extend beyond 12 months
Symptomatic GERD in Adults		20 mg once daily	Up to 4 weeks**
Healing of Duodenal Ulcers		20 mg once daily after the morning meal	Up to 4 weeks***
Helicobacter pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence		Rabeprazole Sodium 20 mg Amoxicillin 1000 mg Clarithromycin 500 mg Take all three medications twice daily with morning and evening meals; it is important that patients comply with the full 7 -day regimen	7 days
Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome		Starting dose 60 mg once daily then adjust to patient needs; some patients require divided doses. Dosages of 100 mg once daily and 60 mg twice daily have been administered	As long as clinically indicated. Some patients with Zollinger -Ellison syndrome have been treated continuously for up to one year
	Adolescents 12 Years of Age and Older		
Symptomatic GERD		20 mg once daily	Up to 8 weeks

* For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of Rabeprazole Gastro-resistant Tablets may be considered.
** If symptoms do not resolve completely after 4 weeks, an additional course of treatment may be considered.
*** Most patients heal within 4 weeks; some patients may require additional therapy to achieve healing.

Administration Instructions
- Swallow Rabeprazole Gastro-resistant Tablets whole. Do not chew, crush, or split tablets.
- For the treatment of duodenal ulcers take Rabeprazole Gastro-resistant Tablets after a meal.
- For Helicobacter pylori eradication take Rabeprazole Gastro-resistant Tablets with food.
- For all other indications Rabeprazole Gastro-resistant Tablets can be taken with or without food.
- Take a missed dose as soon as possible. If it is almost time for the next dose, skip the missed dose and go back to the normal schedule. Do not take two doses at the same time.

4.3 Contraindications
- Rabeprazole Gastro-resistant Tablets are contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles, or to any component of the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute tubulointerstitial nephritis, and urticaria.
- PPIs, including Rabeprazole Gastro-resistant Tablets, are contraindicated with rilpivirine-containing products
- For information about contraindications of antibacterial agents (clarithromycin and amoxicillin) indicated in combination with Rabeprazole Gastro-resistant Tablets, refer to the Contraindications section of their package inserts.

4.4 Special warnings and precautions for use
Presence of Gastric Malignancy
In adults, symptomatic response to therapy with Rabeprazole Gastro-resistant Tablets does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing in adult patients who have a suboptimal response or an early symptomatic relapse after completing treatment with a PPI.

Interaction with Warfarin
Steady state interactions of rabeprazole and warfarin have not been adequately evaluated in patients. There have been reports of increased INR and prothrombin time in patients receiving a proton pump inhibitor and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with Rabeprazole Gastro-resistant Tablets and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Acute Tubulointerstitial Nephritis
Acute tubulointerstitial nephritis (TIN) has been observed in patients taking PPIs and may occur at any point during PPI therapy. Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function (e.g., malaise, nausea, anorexia). In reported case series, some patients were diagnosed on biopsy and in the absence of extra-renal manifestations (e.g., fever, rash or arthralgia).
Discontinue Rabeprazole Gastro-resistant Tablets and evaluate patients with suspected acute TIN.

Clostridium difficile-Associated Diarrhea
Published observational studies suggest that PPI therapy like Rabeprazole Gastro-resistant Tablets may be associated with an increased risk of Clostridium difficile-associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve.
Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.
Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with Rabeprazole Gastro-resistant Tablets.

Bone Fracture
Several published observational studies in adults suggest that PPI 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, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines.

Severe Cutaneous Adverse Reactions
Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with the use of PPIs. Discontinue Rabeprazole Gastro-resistant Tablets at first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

Cutaneous and Systemic Lupus Erythematosus
Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including rabeprazole. These events have occurred as both a new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE.
The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.
Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.
Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving Rabeprazole Gastro-resistant Tablets, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g. ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

Cyanocobalamin (Vitamin B-12) Deficiency
Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed in patients treated with Rabeprazole Gastro-resistant Tablets.

Hypomagnesemia and Mineral Metabolism
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. Hypomagnesemia may lead to hypocalcemia and/or hypokalemia and may exacerbate underlying hypocalcemia in at-risk patients. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.
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.
Consider monitoring magnesium and calcium levels prior to initiation of Rabeprazole Gastro-resistant Tablets and periodically while on treatment in patients with a preexisting risk of hypocalcemia (e.g., hypoparathyroidism). Supplement with magnesium and/or calcium as necessary. If hypocalcemia is refractory to treatment, consider discontinuing the PPI.

Interaction with Methotrexate
Literature suggests that concomitant use of PPIs with methotrexate may elevate and prolong serum concentrations of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients.

Fundic Gland Polyps
PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPI users who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

4.5 Drugs interactions
Table 2 includes drugs with clinically important drug interactions and interaction with diagnostics when administered concomitantly with Rabeprazole Gastro-resistant Tablets and instructions for preventing or managing them.
Consult the labeling of concomitantly used drugs to obtain further information about interactions with PPIs.
Table 2: Clinically Relevant Interactions Affecting Drugs Co-Administered with Rabeprazole Gastro-resistant Tablets and Interactions with Diagnostics

Antiretrovirals	
Clinical Impact:	The effect of PPI on antiretroviral drugs is variable. The clinical importance and the mechanisms behind these interactions are not always known. • Decreased exposure of some antiretroviral drugs (e.g., rilpivirine, atazanavir, and nelfinavir) when used concomitantly with rabeprazole may reduce antiviral effect and promote the development of drug resistance. • Increased exposure of other antiretroviral drugs (e.g., saquinavir) when used concomitantly with rabeprazole may increase toxicity. • There are other antiretroviral drugs which do not result in clinically relevant interactions with rabeprazole.
Intervention:	Rilpivirine-containing products: Concomitant use with Rabeprazole Gastro-resistant Tablets is contraindicated. Atazanavir: See prescribing information for atazanavir for dosing information. Nelfinavir: Avoid concomitant use with Rabeprazole Gastro-resistant Tablets. See prescribing information for nelfinavir. Saquinavir: See the prescribing information for saquinavir and monitor for potential saquinavir toxicities. Other antiretrovirals: See prescribing information.
Warfarin	
Clinical Impact:	Increased INR and prothrombin time in patients receiving PPIs, including rabeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death.
Intervention:	Monitor INR and prothrombin time. Dose adjustment of warfarin may be needed to maintain target INR range. See prescribing inf ormation for warfarin.
Methotrexate	
Clinical Impact:	Concomitant use of rabeprazole with methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. No formal drug interaction studies of methotrexae with PPIs have been conducted.
Intervention:	A temporary withdrawal of Rabeprazole Gastro-resistant Tablets may be considered in some patients receiving high dose methotrexate administration.
Digoxin	
Clinical Impact:	Potential for increased exposure of digoxin
Intervention:	Monitor digoxin concentrations. Dose adjustment of digoxin may be needed to maintain therapeutic drug concentrations. See prescribing information for digoxin.
Drugs Dependent on Gastric pH for Absorption (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole, itraconazole)	
Clinical Impact:	Rabeprazole can reduce the absorption of other drugs due to its effect on reducing intragastric acidity.
Intervention:	Mycophenolate mofetil (MMF): Co-administration of PPIs in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving Rabeprazole Gastro-resistant Tablets and MMF. Use Rabeprazole Gastro-resistant Tablets with caution in transplant patients receiving MMF. See the prescribing information for other drugs dependent on gastric pH for absorption.
Combination Therapy with Clarithromycin and Amoxicillin	
Clinical Impact:	Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions, including potentially fatal arrhythmias, and are contraindicated. Amoxicillin also has drug interactions.
Tacrolimus	
Clinical Impact:	Potentially increased exposure of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.
Intervention:	Monitor tacrolimus whole blood trough concentrations. Dose adjustment of tacrolimus may be needed to maintain therapeutic drug concentrations. See prescribing information for tacrolimus.
Interactions with Investigations of Neuroendocrine Tumors	
Clinical Impact:	Serum chromogranin A (CgA) levels increase secondary to PPI-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors.
Intervention:	Temporarily stop Rabeprazole Gastro-resistant Tablets treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.
Interaction with Secretin Stimulation Test	
Clinical Impact:	Hyper-response in gastrin secretion in response to secretin stimulation test, falsely suggesting gastrinoma.
Intervention:	Temporarily stop treatment with Rabeprazole Gastro-resistant Tablets at least 14 days before assessing to allow gastrin levels to return to baseline.
False Positive Urine Tests for THC	
Clinical Impact:	There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs.
Intervention:	An alternative confirmatory method should be considered to verify positive results.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)
Pregnancy
Risk Summary
There are no available human data on Rabeprazole Gastro-resistant Tablets use in pregnant women to inform the drug associated risk. The background risk of major birth defects and miscarriage for the indicated populations are unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies. No evidence of adverse developmental effects were seen in animal reproduction studies with rabeprazole administered during organogenesis at 13 and 8 times the human area under the plasma concentration-time curve (AUC) at the recommended dose for GERD, in rats and rabbits, respectively.
Changes in bone morphology were observed in offspring of rats treated with oral doses of a different PPI through most of pregnancy and lactation. When maternal administration was confined to gestation only, there were no effects on bone physeal morphology in the offspring at any age.

Data
Animal Data
Embryo-fetal developmental studies have been performed in rats during organogenesis at intravenous doses of rabeprazole up to 50 mg/kg/day (plasma AUC of 11.8 µghr/mL, about 13 times the human exposure at the recommended oral dose for GERD) and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µghr/mL, about 8 times the human exposure at the recommended oral dose for GERD) and have revealed no evidence of harm to the fetus due to rabeprazole.

Administration of rabeprazole to rats in late gestation and during lactation at an oral dose of 400 mg/kg/day (about 195-times the human oral dose based on mg/m^2) resulted in decreases in body weight gain of the pups.

A pre- and postnatal developmental toxicity study in rats with additional endpoints to evaluate bone development was performed with a different PPI at about 3.4 to 57 times an oral human dose on a body surface area basis. Decreased femur length, width and thickness of cortical bone, decreased thickness of the tibial growth plate, and minimal to mild bone marrow hypocellularity were noted at doses of this PPI equal to or greater than 3.4 times an oral human dose on a body surface area basis. Physeal dysplasia in the femur was also observed in offspring after in utero and lactational exposure to the PPI at doses equal to or greater than 33.6 times an oral human dose on a body surface area basis. Effects on maternal bone were observed in pregnant and lactating rats in a pre- and postnatal toxicity study when the PPI was administered at oral doses of 3.4 to 57 times an oral human dose on a body surface area basis. When rats were dosed from gestational day 7 through weaning on postnatal day 21, a statistically significant decrease in maternal femur weight of up to 14% (as compared to placebo treatment) was observed at doses equal to or greater than 33.6 times an oral human dose on a body surface area basis.

A follow-up developmental toxicity study in rats with further time points to evaluate pup bone development from postnatal day 2 to adulthood was performed with a different PPI at oral doses of 280 mg/kg/day (about 68 times an oral human dose on a body surface area basis) where drug administration was from either gestational day 7 or gestational day 16 until parturition. When maternal administration was confined to gestation only, there were no effects on bone physeal morphology in the offspring at any age.

Lactation
Risk Summary
Lactation studies have not been conducted to assess the presence of rabeprazole in human milk, the effects of rabeprazole on the breastfed infant, or the effects of rabeprazole on milk production. Rabeprazole is present in rat milk. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for Rabeprazole Gastro-resistant Tablets and any potential adverse effects on the breastfed infant from Rabeprazole Gastro-resistant Tablets or from the underlying maternal condition.

Pediatric Use
The safety and effectiveness of Rabeprazole Gastro-resistant Tablets have been established in pediatric patients for adolescent patients 12 years of age and older for the treatment of symptomatic GERD. Use of Rabeprazole Gastro-resistant Tablets in this age group is supported by adequate and well controlled studies in adults and a multicenter, randomized, open-label, parallel-group study in 111 adolescent patients 12 to 16 years of age. Patients had a clinical diagnosis of symptomatic GERD, or suspected or endoscopically proven GERD and were randomized to either 10 mg or 20 mg once daily for up to 8 weeks for the evaluation of safety and efficacy. The adverse reaction profile in adolescent patients was similar to that of adults. The related reported adverse reactions that occurred in ≥2% of patients were headache (5%) and nausea (2%). There were no adverse reactions reported in these studies that were not previously observed in adults.

The safety and effectiveness of Rabeprazole Gastro-resistant Tablets have not been established in pediatric patients for:
- Healing of Erosive or Ulcerative GERD
- Maintenance of Healing of Erosive or Ulcerative GERD
- Treatment of Symptomatic GERD
- Healing of Duodenal Ulcers
- Helicobacter pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence
- Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome

Rabeprazole Gastro-resistant Tablets are not recommended for use in pediatric patients less than 12 years of age because the tablet strength exceeds the recommended dose for these patients. For pediatric patients 1 year to less than 12 years of age consider another rabeprazole formulation. The safety and effectiveness of a different dosage form and dosage strength of rabeprazole has been established in pediatric patients 1 to 11 years for the treatment of GERD.

Juvenile Animal Data
Studies in juvenile and young adult rats and dogs were performed. In juvenile animal studies rabeprazole sodium was administered orally to rats for up to 5 weeks and to dogs for up to 13 weeks, each commencing on Day 7 post-partum and followed by a 13-week recovery period. Rats were dosed at 5, 25, or 150 mg/kg/day and dogs were dosed at 3, 10, or 30 mg/kg/day. The data from these studies were comparable to those reported for young adult animals. Pharmacologically mediated changes, including increased serum gastrin levels and stomach changes, were observed at all dose levels in both rats and dogs. These observations were reversible over the 13-week recovery periods. Although body weights and/or crown-rump lengths were minimally decreased during dosing, no effects on the development parameters were noted in either juvenile rats or dogs.

When juvenile animals were treated for 28 days with a different PPI at doses equal to or greater than 34 times the daily oral human dose on a body surface area basis, overall growth was affected and treatment-related decreases in body weight (approximately 14%) and body weight gain, and decreases in femur weight and femur length were observed.

Geriatric Use
Of the total number of subjects (n=2009) in clinical studies of Rabeprazole Gastro-resistant Tablets, 19% were 65 years and over, while 4% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment
Administration of Rabeprazole Gastro-resistant Tablets to patients with mild to moderate hepatic impairment (Child-Pugh Class A and B, respectively) resulted in increased exposure and decreased elimination. No dosage adjustment is necessary in patients with mild to moderate hepatic impairment. There is no information in patients with severe hepatic impairment (Child-Pugh Class C). Avoid use of Rabeprazole Gastro-resistant Tablets in patients with severe hepatic impairment; however, if treatment is necessary, monitor patients for adverse reactions.

4.7 Effects on ability to drive and use machines
Based on the pharmacodynamic properties and the adverse events profile, it is unlikely that Rabeprazole Gastro-resistant Tablets 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
The following serious adverse reactions are described below and elsewhere in labeling:
- ***Acute kidney injury***
- Acute Tubulointerstitial Nephritis
- Clostridium difficile-Associated Diarrhea
- Bone Fracture
- Severe Cutaneous Adverse Reactions
- Cutaneous and Systemic Lupus Erythematosus
- Cyanocobalamin (Vitamin B-12) Deficiency
- Hypomagnesemia and Mineral Metabolism
- Fundic Gland Polyps

Clinical Studies Experience
Because clinical trials are conducted under varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults
The data described below reflect exposure to Rabeprazole Gastro Resistant-resistant Tablets in 1064 adult patients exposed for up to 8 weeks. The studies were primarily placebo- and active-controlled trials in adult patients with Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD), Duodenal Ulcers and Gastric Ulcers. The population had a mean age of 53 years (range 18-89 years) and had a ratio of approximately 60% male: 40% female. The racial distribution was 86% Caucasian, 8% African American, 2% Asian, and 5% other. Most patients received either 10 mg, 20 mg or 40 mg per day of Rabeprazole Gastro Resistant-resistant Tablets.

An analysis of adverse reactions appearing in ≥2% of patients treated with Rabeprazole Gastro-resistant Tablets (n=1064) and with a greater frequency than placebo (n=89) in controlled North American and European acute treatment trials, revealed the following adverse reactions: pain (3% vs. 1%), pharyngitis (3% vs. 2%), flatulence (3% vs. 1%), infection (2% vs. 1%), and constipation (2% vs. 1%).

Three long-term maintenance studies consisted of a total of 740 adult patients; at least 54% of adult patients were exposed to Rabeprazole Gastro-resistant Tablets for 6 months and at least 33% were exposed for 12 months. Of the 740 adult patients, 247 (33%) and 241 (33%) patients received 10 mg and 20 mg of Rabeprazole Gastro-resistant Tablets, respectively, while 169 (23%) patients received placebo and 83 (11%) received omeprazole.
The safety profile of rabeprazole in the maintenance studies in adults was consistent with what was observed in the acute studies.

Less common adverse reactions seen in controlled clinical trials (<2% of patients treated with Rabeprazole Gastro-resistant Tablets and greater than placebo) and for which there is a possibility of a causal relationship to rabeprazole, include the following: headache, abdominal pain, diarrhea, dry mouth, dizziness, peripheral edema, hepatic enzyme increase, hepatitis, hepatic encephalopathy, myalgia, and arthralgia.

Combination Treatment with Amoxicillin and Clarithromycin: In clinical trials using combination therapy with rabeprazole plus amoxicillin and clarithromycin (RAC), no adverse reactions unique to this drug combination were observed. In the U.S. multicenter study, the most frequently reported drug related adverse reactions for patients who received RAC therapy for 7 or 10 days were diarrhea (8% and 7%) and taste perversion (6% and 10%), respectively.
No clinically significant laboratory abnormalities particular to the drug combinations were observed.

Pediatrics
In a multicenter, open-label study of adolescent patients 12 to 16 years of age with a clinical diagnosis of symptomatic GERD or endoscopically proven GERD, the adverse event profile was similar to that of adults. The adverse reactions reported without regard to relationship to Rabeprazole Gastro-resistant Tablets that occurred in ≥2% of 111 patients were headache (9.9%), diarrhea (4.5%), nausea (4.5%), vomiting (3.6%), and abdominal pain (3.6%). The related reported adverse reactions that occurred in ≥2% of patients were headache (5.4%) and nausea (1.8%). There were no adverse reactions reported in this study that were not previously observed in adults.

Postmarketing Experience
The following adverse reactions have been identified during post approval use of rabeprazole.
Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:
Blood and Lymphatic System Disorders: agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia
Ear and Labyrinth Disorders: vertigo
Eye Disorders: blurred vision
Gastrointestinal Disorders: fundic gland polyps
General Disorders and Administration Site Conditions: sudden death
Hepatobiliary Disorders: jaundice
Immune System Disorders: anaphylaxis, angioedema, systemic lupus erythematosus, Stevens Johnson syndrome, toxic epidermal necrolysis (some fatal), DRESS, AGEP
Infections and Infestations: Clostridium difficile-associated diarrhea
Investigations: Increases in prothrombin time/INR (in patients treated with concomitant warfarin), TSH elevations

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Metabolism and Nutrition Disorders: hyperammonemia, hypomagnesemia, hypocalcemia, Hypokalemia, hyponatremia
Musculoskeletal System Disorders: bone fracture, rhabdomyolysis
Nervous System Disorders: coma
Psychiatric Disorders: delirium, disorientation
Renal and Urinary Disorders: interstitial nephritis
Respiratory, Thoracic and Mediastinal Disorders: interstitial pneumonia
Skin and Subcutaneous Tissue Disorders: severe dermatologic reactions including bullous and other drug eruptions of the skin, cutaneous lupus erythematosus, erythema multiforme

4.9 Overdose
Seven reports of accidental overdosage with rabeprazole have been received. The maximum reported overdose was 80 mg. There were no clinical signs or symptoms associated with any reported overdose. Patients with Zollinger-Ellison syndrome have been treated with up to 120 mg rabeprazole once daily. No specific antidote for rabeprazole is known. Rabeprazole is extensively protein bound and is not readily dialyzable.
In the event of overdosage, treatment should be symptomatic and supportive.

5. Pharmacological properties
5.1 Mechanism of Action
Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole proton-pump inhibitors) that do not exhibit anticholinergic or histamine H_2-receptor antagonist properties but suppress gastric acid secretion by inhibiting the gastric H^+, K^+ ATPase at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, rabeprazole has been characterized as a gastric proton-pump inhibitor. Rabeprazole blocks the final step of gastric acid secretion.
In gastric parietal cells, rabeprazole is protonated, accumulates, and is transformed to an active sulfenamide. When studied *in vitro*, rabeprazole is chemically activated at pH 1.2 with a half-life of 78 seconds. It inhibits acid transport in porcine gastric vesicles with a half-life of 90 seconds.

5.2 Pharmacodynamic properties
Antisecretory Activity
The antisecretory effect begins within one hour after oral administration of 20 mg Rabeprazole Gastro-resistant Tablets. The median inhibitory effect of rabeprazole on 24 hour gastric acidity is 88% of maximal after the first dose. A 20 mg dose of Rabeprazole Gastro-resistant Tablets inhibits basal and peptone meal-stimulated acid secretion versus placebo by 86% and 95%, respectively, and increases the percent of a 24-hour period that the gastric pH>3 from 10% to 65% (see table
below). This relatively prolonged pharmacodynamic action compared to the short pharmacokinetic half-life (1 to 2 hours) reflects the sustained inactivation of the H^+, K^+ ATPase.
Table 3: Gastric Acid Parameters: Rabeprazole Gastro-resistant Tablets versus Placebo After 7 Days of Once Daily Dosing

Parameter	Rabeprazole Gastro-resistant Tablets (20 mg once daily)	Placebo
Basal Acid Output (mmol/hr)	0.4*	2.8
Stimulated Acid Output (mmol/hr)	0.6*	13.3
% Time Gastric pH>3	65*	10

*(p<0.01 versus placebo)

Compared to placebo, 10 mg, 20 mg, and 40 mg of Rabeprazole Gastro-resistant Tablets, administered once daily for 7 days significantly decreased intragastric acidity with all doses for each of four meal-related intervals and the 24-hour time period overall. In this study, there were no statistically significant differences between doses; however, there was a significant dose-related decrease in intragastric acidity. The ability of rabeprazole to cause a dose-related decrease in mean intragastric acidity is illustrated below.

Table 4: AUC Acidity (MmolHr/L): Rabeprazole Gastro-resistant Tablets versus Placebo on Day 7 of Once Daily Dosing (Mean±SD)

AUC interval (hrs)	Rabeprazole Gastro-resistant Tablets			
	10 mg (N=24)	20 mg (N=24)	40 mg (N=24)	Placebo (N=24)
08:00 – 13:00	19.6±21.5*	12.9±23*	7.6±14.7*	91.1±39.7
13:00 – 19:00	5.6±9.7*	8.3±29.8*	1.3±5.2*	95.5±48.7
19:00 – 22:00	0.1±0.1*	0.1±0.06*	0.0±0.02*	11.9±12.5
22:00 – 08:00	129.2±84*	109.6±67.2*	76.9±58.4*	479.9±165
AUC 0-24 hours	155.5±90.6*	130.9±81*	85.8±64.3*	678.5±216

*(p<0.001 versus placebo)

After administration of 20 mg Rabeprazole Gastro-resistant Tablets once daily for eight days, the mean percent of time that gastric pH greater than 3 or gastric pH greater than 4 after a single dose (Day 1) and multiple doses (Day 8) was significantly greater than placebo. The decrease in gastric acidity and the increase in gastric pH observed with 20 mg Rabeprazole Gastro-resistant Tablets administered once daily for eight days were compared to the same parameters for placebo, as illustrated below:

Table 5: Gastric Acid Parameters Rabeprazole Gastro-resistant Tablets Once Daily Dosing versus Placebo on Day 1 and Day 8

Parameter	Rabeprazole Gastro-resistant Tablets 20 mg once daily		Placebo	
	Day 1	Day 8	Day 1	Day 8
Mean AUC_{0-24} Acidity	340.8*	176.9*	925.5	862.4
Median trough pH (23-hr)[a]	3.77	3.51	1.27	1.38
% Time Gastric pH greater than 3[b]	54.6*	68.7*	19.1	21.7
% Time Gastric pH greater than 4[b]	44.1*	60.3*	7.6	11.0

[a] No inferential statistics conducted for this parameter.
[b] Gastric pH was measured every hour over a 24-hour period.
* (p<0.001 versus placebo)

Effects on Esophageal Acid Exposure
In patients with GERD and moderate to severe esophageal acid exposure, a dose of 20 mg and 40 mg per day of Rabeprazole Gastro-resistant Tablets decreased 24-hour esophageal acid exposure. After seven days of treatment, the percentage of time that the esophageal pH was less than 4 decreased from baselines of 24.7% for 20 mg and 23.7% for 40 mg, to 5.1% and 2.0%, respectively. Normalization of 24-hour intraesophageal acid exposure was correlated to gastric pH greater than 4 for at least 35% of the 24-hour period; this level was achieved in 90% of subjects receiving Rabeprazole Gastro-resistant Tablets 20 mg and in 100% of subjects receiving Rabeprazole Sodium 40 mg. With Rabeprazole Gastro-resistant Tablets 20 mg and 40 mg per day, significant effects on gastric and esophageal pH were noted after one day of treatment, and more pronounced after seven days of treatment.

Effects on Serum Gastrin
The median fasting gastrin level increased in a dose-related manner in patients treated once daily with Rabeprazole Gastro-resistant Tablets for up to eight weeks for ulcerative or erosive esophagitis and in patients treated for up to 52 weeks to prevent recurrence of disease. The group median values stayed within the normal range.

In a group of subjects treated with 20 mg Rabeprazole Gastro-resistant Tablets for 4 weeks a doubling of mean serum gastrin concentrations was observed. Approximately 35% of these treated subjects developed serum gastrin concentrations above the upper limit of normal.

Effects on Enterochromaffin-like (ECL) Cells
Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially in females.

In over 400 patients treated with Rabeprazole Gastro-resistant Tablets (10 or 20 mg) once daily for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumors observed in rats.

Endocrine Effects
Studies in humans for up to one year have not revealed clinically significant effects on the endocrine system. In healthy male subjects treated with Rabeprazole Gastro-resistant Tablets for 13 days, no clinically relevant changes have been detected in the following endocrine parameters examined: 17 -estradiol, thyroid stimulating hormone, tri-iodothyronine, thyroxine, thyroxine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteotrophic hormone, prolactin, somatotrophic hormone, dehydroepiandrosterone, cortisol-binding globulin, and urinary 6-hydroxycortisol, serum testosterone and circadian cortisol profile.

Other Effects
In humans treated with Rabeprazole Gastro-resistant Tablets for up to one year, no systemic effects have been observed on the central nervous, lymphoid, hematopoietic, renal, hepatic, cardiovascular, or respiratory systems. No data are available on long-term treatment with Rabeprazole Gastro-resistant Tablets and ocular effects.

5.3 Pharmacokinetic properties
After oral administration of 20 mg Rabeprazole Gastro-resistant Tablets, peak plasma concentrations (C_{max}) of rabeprazole occur over a range of 2 to 5 hours (T_{max}). The rabeprazole C_{max} and AUC are linear over an oral dose range of 10 mg to 40 mg. There is no appreciable accumulation when doses of 10 mg to 40 mg are administered every 24 hours; the pharmacokinetics of rabeprazole is not altered by multiple dosing.

Absorption
Absolute bioavailability for a 20 mg oral tablet of rabeprazole (compared to intravenous administration) is approximately 52%. When Rabeprazole Gastro-resistant Tablets are administered with a high fat meal, T_{max} is variable; which concomitant food intake may delay the absorption up to 4 hours or longer. However, the C_{max} and the extent of rabeprazole absorption (AUC) are not significantly altered. Thus, Rabeprazole Gastro-resistant Tablets may be taken without regard to timing of meals.

Distribution
Rabeprazole is 96.3% bound to human plasma proteins.

Elimination
Metabolism:
Rabeprazole is extensively metabolized. A significant portion of rabeprazole is metabolized via systemic nonenzymatic reduction to a thioether compound. Rabeprazole is also metabolized to sulphone and desmethyl compounds via cytochrome P450 in the liver. The thioether and sulphone are the primary metabolites measured in human plasma. These metabolites were not observed to have significant antisecretory activity. *In vitro* studies have demonstrated that rabeprazole is metabolized in the liver primarily by cytochromes P450 3A (CYP3A) to a sulphone metabolite and cytochrome P450 2C19 (CYP2C19) to desmethyl rabeprazole. CYP2C19 exhibits a known genetic polymorphism due to its deficiency in some sub-populations (e.g., 3 to 5% of Caucasians and 17 to 20% of Asians). Rabeprazole metabolism is slow in these sub-populations, therefore, they are referred to as poor metabolizers of the drug.

Excretion:
Following a single 20 mg oral dose of ^{14}C-labeled rabeprazole, approximately 90% of the drug was eliminated in the urine, primarily as thioether carboxylic acid; its glucuronide, and mercapturic acid metabolites. The remainder of the dose was recovered in the feces. Total recovery of radioactivity was 99.8%. No unchanged rabeprazole was recovered in the urine or feces.

Specific Populations
Geriatric Patients:
In 20 healthy elderly subjects administered 20 mg Rabeprazole Gastro-resistant Tablets once daily for seven days, AUC values approximately doubled and the C_{max} increased by 60% compared to values in a parallel younger control group. There was no evidence of drug accumulation after once daily administration.

Pediatric Patients:
The pharmacokinetics of rabeprazole was studied in 12 adolescent patients with GERD 12 to 16 years of age, in a multicenter study. Patients received 20 mg Rabeprazole Gastro-resistant Tablets once daily for five or seven days. An approximate 40% increase in rabeprazole exposure was noted following 5 to 7 days of dosing compared with the exposure after 1 day dosing. Pharmacokinetic parameters in adolescent patients with GERD 12 to 16 years of age were within the range observed in healthy adult subjects.

Male and Female Patients and Racial or Ethnic Groups:
In analyses adjusted for body mass and height, rabeprazole pharmacokinetics showed no clinically significant differences between male and female subjects. In studies that used different formulations of rabeprazole, AUC_0, values for healthy Japanese men were approximately 50 to 60% greater than values derived from pooled data from healthy men in the United States.

Patients with Renal Impairment:
In 10 patients with stable end-stage renal disease requiring maintenance hemodialysis (creatinine clearance 5 mL/min/1.73 m^2), no clinically significant differences were observed in the pharmacokinetics of rabeprazole after a single 20 mg dose Rabeprazole Gastro-resistant Tablets when compared to 10 healthy subjects.

Patients with Hepatic Impairment:
In a single dose study of 10 patients with mild to moderate hepatic impairment (Child-Pugh Class A and B, respectively) who were administered a single 20 mg dose of Rabeprazole Gastro-resistant Tablets, AUC_{0-24} was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg Rabeprazole Gastro-resistant Tablets once daily for eight days, AUC_0, and C_{max} values increased approximately 20% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.
No information exists on rabeprazole disposition in patients with severe hepatic impairment (Child-Pugh Class C)

Drug Interaction Studies
Combined Administration with Antimicrobials:
Sixteen healthy subjects genotyped as extensive metabolizers with respect to CYP2C19 were given 20 mg Rabeprazole Gastro-resistant Tablets, 1000 mg amoxicillin, 500 mg clarithromycin, or all 3 drugs in a four-way crossover study. Each of the four regimens was administered twice daily for 6 days. The AUC and C_{max} for clarithromycin and amoxicillin were not different following combined administration compared to values following single administration. However, the rabeprazole AUC and C_{max} increased by 11% and 34%, respectively, following combined administration. The AUC and C_{max} for 14-hydroxyclarithromycin (active metabolite of clarithromycin) also increased by 42% and 46%, respectively. This increase in exposure to rabeprazole and 14-hydroxyclarithromycin is not expected to produce safety concerns.

Effects of Other Drugs on Rabeprazole
Antacids: Co-administration of Rabeprazole Gastro-resistant Tablets and antacids produced no clinically relevant changes in plasma rabeprazole concentrations.

Effects of Rabeprazole on Other Drugs
Studies in healthy subjects have shown that rabeprazole does not have clinically significant interactions with other drugs metabolized by the CYP450 system, such as theophylline (CYP1A2) given as single oral doses, diazepam (CYP2C9 and CYP3A4) as a single intravenous dose, and phenytoin (CYP2C9 and CYP2C19) given as a single intravenous dose (with supplemental oral dosing). Steady state interactions of rabeprazole and other drugs metabolized by this enzyme system have not been studied in patients.

Clopidogrel: Clopidogrel is metabolized to its active metabolite in part by CYP2C19. A study of healthy subjects including CYP2C19 extensive and intermediate metabolizers receiving once daily administration of clopidogrel 75 mg concomitantly with placebo or with 20 Rabeprazole Gastro-resistant Tablets (n=36), for 7 days was conducted. The mean AUC of the active metabolite of clopidogrel was reduced by approximately 12% (mean AUC ratio was 88%, with 90% CI of 81.7 to 95.5%) when Rabeprazole Gastro-resistant Tablets were coadministered compared to administration of clopidogrel with placebo.

Digoxin: In healthy adult subjects (n=16), co-administration of 20 mg Rabeprazole Gastro-resistant Tablets with 2.5 mg once daily doses of digoxin at steady state resulted in approximately 29% and 19% increase in mean C_{max} and $AUC_{(0-24)}$ of digoxin.

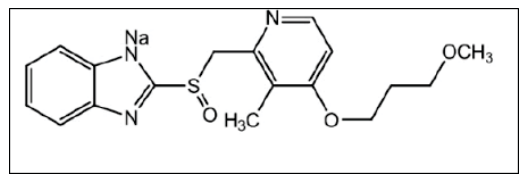
Ketoconazole: In healthy adult subjects (n=19), co-administration of 20 mg Rabeprazole Gastro-resistant Tablets at steady state with a single 400 mg oral dose ketoconazole resulted in approximately an average of 31% reduction in both C_{max} and $AUC_{(0-inf)}$ of ketoconazole.

Cyclosporine: In vitro incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporine metabolism with an IC_{50} of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days of dosing with 20 mg of Rabeprazole Gastro-resistant Tablets. This degree of inhibition is similar to that by omeprazole at equivalent concentrations.

6. Nonclinical properties
6.1 Animal Toxicology or Pharmacology
Carcinogenesis, Mutagenesis, Impairment of Fertility
In an 88/104-week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumor occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 µghr/mL which is 1.6 times the human exposure (plasma AUC_0 = 0.88 µghr/mL) at the recommended dose for GERD (20 mg/day). In a 28-week carcinogenicity study in p53+/- transgenic mice, rabeprazole at oral doses of 20, 60, and 200 mg/kg/day did not cause an increase in the incidence rates of tumors but produced gastric mucosal hyperplasia at all doses. The systemic exposure to rabeprazole at 200 mg/kg/day is about 17 to 24 times the human exposure at the recommended dose for GERD. In a 104-week carcinogenicity study in Sprague-Dawley rats, males were treated with oral doses of 5, 15, 30 and 60 mg/kg/day and females with 5, 15, 30, 60, and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumors in female rats at all doses including the lowest tested dose. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 µghr/mL which is about 0.1 times the human exposure at the recommended dose for GERD. In male rats, no treatment related tumors were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 µghr/mL (0.2 times the human exposure at the recommended dose for GERD).

Rabeprazole was positive in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward gene mutation test, and the mouse lymphoma cell (L5178Y/TK+/–) forward gene mutation test. Its demethylated-metabolite was also positive in the Ames test. Rabeprazole was negative in the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test, and the *in vivo* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests. Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 µghr/mL, about 10 times the human exposure at the recommended dose for GERD) was found to have no effect on fertility and reproductive performance of male and female rats.

7. Description
The active ingredient in Rabeprazole Gastro-resistant Tablets is rabeprazole sodium, which is a proton pump inhibitor. It is a substituted benzimidazole known chemically as 2-[[[4-(3 methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1H–benzimidazole sodium salt. It has an empirical formula of $C_{18}H_{20}N_3NaO_3S$ and a molecular weight of 381.42. Rabeprazole sodium is a white to slightly yellowish-white solid. It is very soluble in water and methanol, freely soluble in ethanol, chloroform, and ethyl acetate and insoluble in ether and n-hexane. The stability of rabeprazole sodium is a function of pH; it is rapidly degraded in acid media, and is more stable under alkaline conditions. The structural figure is:



8. Pharmaceutical particulars
8.1 Incompatibilities
NA

8.2 Shelf-life
Please refer to details on blister/carton.

8.3 Packaging information
Alu-Alu blister of 10's tablets.

8.4 Storage and handing instructions
Store protected from light & moisture at a temperature not exceeding 25ºC.

9. Patient Counselling Information
Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is Rabeprazole Gastro-resistant Tablets?
Rabeprazole Gastro-resistant Tablets is a prescription medicine called a proton pump inhibitor (PPI). Rabeprazole Gastro-resistant Tablets reduce the amount of acid in your stomach.In adults Rabeprazole Gastro-resistant Tablets is used for:

8 weeks up to 16 weeks to heal acid-related damage to the lining of the esophagus (called erosive esophagitis or EE) and to relieve symptoms, such as heartburn pain.
- maintaining healing of the esophagus and relief of symptoms related to EE. It is not known if Rabeprazole Gastro-resistant Tablets are safe and effective if used longer than 12 months (1 year).
- up to 4 weeks to treat daytime and nighttime heartburn and other symptoms that happen with Gastroesophageal Reflux Disease (GERD).
- up to 4 weeks for the healing and relief of symptoms of duodenal ulcers.
- 7 days with certain antibiotic medicines to treat an infection and stomach (duodenal) ulcers caused by bacteria called H. pylori.
- the long-term treatment of conditions where your stomach makes too much acid. This includes a rare condition called Zollinger-Ellison syndrome.

In adolescents 12 years of age and older:

Rabeprazole Gastro-resistant Tablets are used for up to 8 weeks to treat symptoms of GERD. It is not known if Rabeprazole Gastro-resistant Tablets are safe and effective in children less than 12 years of age for other uses. Rabeprazole Gastro-resistant Tablets should not be used in children under 12 years of age.

Who should not take Rabeprazole Gastro-resistant Tablets?
Do not take **Rabeprazole Gastro-resistant Tablets**, if you:

- allergic to rabeprazole, any other PPI medicine, or any of the ingredients in Rabeprazole Gastro-resistant Tablets. See the end of this Medication Guide for a complete list of ingredients.
- taking medicine that contains rilpivirine (EDURANT, COMPLERA, ODEFSEY) used to treat HIV-1 (Human Immunodeficiency Virus).

What should I tell my doctor before taking take Rabeprazole Gastro-resistant Tablets?

Tell your doctor about all of your medical problems, including if you:
- If you have low magnesium levels, low calcium levels and low potassium levels in your blood.
- If you have liver problems.
- If you are pregnant or plan to become pregnant. It is not known if Rabeprazole Gastro-resistant Tablets can harm your unborn baby.
- If you are breastfeeding or plan to breastfeed. It is not known if Rabeprazole Gastro-resistant Tablets passes into your breast milk. Talk to your doctor about the best way to feed your baby if you take Rabeprazole Gastro-resistant Tablets.

Tell your doctor about all the medicines you take
including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your doctor if you take an antibiotic that contains clarithromycin or amoxicillin or if you take warfarin (COUMADIN, JANTOVEN), methotrexate (OTREXUP, RASUVO, TREXALL, XATMEP), digoxin (LANOXIN), or a water pill (diuretic).

How should I take Rabeprazole Gastro-resistant Tablets
Take Rabeprazole Gastro-resistant Tablets exactly as prescribed.
- Rabeprazole Gastro-resistant Tablets are usually taken 1 time each day. Your doctor will tell you the time of day to take Rabeprazole Gastro-resistant Tablets, based on your medical condition.
- Rabeprazole Gastro-resistant Tablets can be taken with or without food. Your doctor will tell you whether to take this medicine with or without food based on your medical condition.
- Swallow each Rabeprazole Gastro-resistant Tablets whole. Do not chew, crush, or split Rabeprazole Gastro-resistant Tablets. Tell your doctor if you cannot swallow tablets whole.
- If you miss a dose of Rabeprazole Gastro-resistant Tablets, take it as soon as possible. If it is almost time for your next dose, you should not take the missed dose. You should take your next dose at your regular time. Do not take 2 doses at the same time.
- If your doctor prescribes antibiotic medicines with Rabeprazole Gastro-resistant Tablets, read the patient information that comes with the antibiotic medicines before you take them.

What are possible side effects of Rabeprazole Gastro-resistant Tablets?
Rabeprazole Gastro-resistant Tablets can cause serious side effects, including:
➢ **Interaction with warfarin:** Taking warfarin with a PPI medicine may lead to an increased risk of bleeding and death. If you take warfarin, your doctor may check your blood to see if you have an increased risk of bleeding. If you take warfarin during treatment with Rabeprazole Gastro-resistant Tablets, tell your doctor right away if you have any signs or symptoms of bleeding, including:

- Pain, swelling or discomfort
- Headaches, dizziness, or weakness
- unusual bruising (bruises that happen without known cause or that grow in size)
- nosebleeds
- bleeding gums
- bleeding from cuts take a long time to stop
- menstrual bleeding that is heavier than normal
- pink or brown urine
- red or black stools
- coughing up blood
- vomiting blood or vomit that looks like coffee grounds

➢ **Low vitamin B-12 levels:** in the body can happen in people who have taken Rabeprazole Gastro-resistant Tablets for a long time (more than 3 years). Tell your doctor if you have symptoms of low vitamin B-12 levels, including shortness of breath, lightheadedness, irregular heartbeat, muscle weakness, pale skin, feeling tired, mood changes, and tingling or numbness in the arms and legs.
➢ **Low magnesium levels in the body**: can happen in people who have taken Rabeprazole Gastro-resistant Tablets for at least 3 months. Tell your doctor if you have symptoms of low magnesium levels, including seizures, dizziness, irregular heartbeat, jitteriness, muscle aches or weakness, and spasms of hands, feet or voice.

➢ **Stomach growths (fundic gland polyps):** People who take PPI medicines for a long time have an increased risk of developing a certain type of stomach growths called fundic gland polyps, especially after taking PPI medicines for more than 1 year.

➢ **Severe skin reactions:** Rabeprazole Gastro-resistant Tabletscan cause rare but serious skin reactions that may affect any part of your body. These serious skin reactions may need to be treated in a hospital and may be life threatening:

- Skin rash which may have blistering, peeling or bleeding on any part of your skin (including your lips, eyes, mouth, nose, genitals, hands or feet).
- You may also have fever, chills, body aches, shortness of breath, or enlarged lymph nodes. Stop taking Rabeprazole Gastro-resistant Tablets and call your doctor right away. These symptoms may be the first sign of a severe skin reaction.

➢ Rabeprazole Gastro-resistant Tablets can cause Acute kidney injury.

➢ **The most common side effects of Rabeprazole Gastro-resistant Tablets in adults include** pain, sore throat, infection, and constipation.

➢ **The most common side effects Rabeprazole Gastro-resistant Tablets in adolescents 12 years of age and older include:** headache, diarrhea, nausea, vomiting, and stomach-area (abdomen) pain.

10. Details of manufacturer
Windlas Biotech Limited (Plant-3),
Plot No. 39, Pharmacity, Selaqui,
Dehradun-248197, Uttarakhand

11. Details of permission or licence number with date
Licence No.: 30/UA/2020 **Dated:** 27/08/2022

12. Date of revision
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The Nexus of Health and Innovation
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Maharashtra-411017

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