Acilesol
Gastro-resistant tablet
(Rabeprazole sodium)

1. TRADE NAME OF THE MEDICINAL PRODUCT
ACILESOL TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One tablet contains
9.42 mg rabeprazole as 10 mg rabeprazole sodium
18.85 mg rabeprazole as 20 mg rabeprazole sodium

3. PHARMACEUTICAL FORM
Gastro-resistant tablets.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
ACILESOL tablets are indicated for the treatment of:

- Prevention of gastric and duodenal ulcer recurrences associated with low-dose aspirin therapy
- Active duodenal ulcer
- Active benign gastric ulcer
- Symptomatic erosive or ulcerative gastro-esophageal reflux disease (GERD)
- Gastro-esophageal Reflux Disease Long-term Management (GERD Maintenance)
- Symptomatic treatment of moderate to very severe gastro-esophageal reflux disease (symptomatic GERD)
- 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:

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

Active Duodenal Ulcer, Active Benign Gastric Ulcer and Erosive or Ulcerative Gastro-Esophageal Reflux Disease (GERD): The usual adult dose is 10mg rabeprazole sodium administered orally once daily. However, the dosage may be increased up to 20mg orally once a day depending on severity of symptoms. For the treatment of active benign gastric ulcer and symptomatic erosive or ulcerative GERD, the usual administration should be restricted to up to 8 weeks, and for active duodenal ulcer, 6 weeks.

A dose of 10mg twice daily for a further 8 weeks may be administered orally to reflux esophagitis patients who do not respond to usual doses of proton pump inhibitor treatment. However, dose of 20mg twice daily may be administered to patients with severe mucosa injury.

Gastro-Esophageal Reflux Disease Long-term Management (GERD Maintenance):
For long-term management, a maintenance dose of Rabeprazole 20 mg or 10 mg once daily can be used depending upon patient response.

For the maintenance therapy of reflux esophagitis when proton pump inhibitor treatment is ineffective, dose of 10 mg twice daily may be administered orally.

Symptomatic treatment of moderate to very severe gastro-esophageal reflux disease (symptomatic GERD): 10mg 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 10mg once daily when needed.

Eradication of H. pylori: Patients with *H. pylori* infection should be treated with eradication therapy. The following combination given for 7 days is recommended.
Rabeprazole 20mg twice daily + clarithromycin 500mg twice daily and amoxicillin 1g twice daily

For indications requiring once daily treatment ACILESOL tablets 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 ACILESOL tablets 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.
See section 4.4 Special Warnings and Precautions for Use of rabeprazole in the treatment of patients with severe hepatic impairment.

Children:
Rabeprazole is not recommended for use in children, as there is no experience of its use in this group.

4.3 Contraindications:
Rabeprazole is contra-indicated in patients with known hypersensitivity to rabeprazole sodium, substituted benzimidazoles or to any excipient used in the formulation. Rabeprazole 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 or malignancy should be excluded prior to commencing treatment with rabeprazole.

For prevention of gastric and duodenal ulcer recurrences associated with low-dose aspirin therapy, administer rabeprazole in patients who are continuously receiving low-dose aspirin to prevent thrombosis or embolism formation, and confirm whether the patient has a history of gastric ulcer or duodenal ulcer before starting administration.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Bone Fracture: Several published observational studies suggest that proton pump inhibitor (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.

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with the proton pump inhibitors (PPIs) for at least three months, in most cases after a year of therapy. Rabeprazole is the member of PPIs. Serious adverse events include tetany, arrhythmias and seizures. 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.

No evidence of significant drug related safety problems was seen in a study of patients with mild to moderate hepatic impairment versus normal age and sex matched controls. However because there are no clinical data on the use of rabeprazole tablets in the treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with rabeprazole is first initiated in such patients.

Published observational studies suggest that proton pump inhibitor (PPI) therapy like Rabeprazole Tablets may be associated with an increased risk of *Clostridium difficile* associated diarrhea (CDAD), especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve (see section 4.8).

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

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 Tablets, refer to WARNINGS and PRECAUTIONS sections of those package inserts.

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels 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 (see section 4.5)

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs. These events have occurred as both 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 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., Antinuclear antibody) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

Long term PPI use, including rabeprazole, appears to be associated with an increased risk of fundic gland polyps. Most fundic gland polyps are asymptomatic. Patients with large or ulcerated polyps may be at risk of gastrointestinal bleeding or small intestinal blockage. Use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

4.5 Interaction with other Medicaments and other forms of Interaction
Rabeprazole sodium, as is the case with other members of PPI class of compounds, is metabolized through the cytochrome P450 (CYP450) hepatic drug metabolizing system. Studies in healthy subjects have shown that rabeprazole sodium does not have clinically significant interactions with the drugs studied including warfarin, phenytoin, theophylline or diazepam metabolized by the CYP450 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, therefore the potential for such interaction was investigated. Co-administration of rabeprazole sodium results in a 33% decrease in ketoconazole levels and a 22% increase in trough digoxin levels in normal subjects. Therefore individual patients may need to be monitored to determine if a dosage adjustment is necessary when such drugs are taken concomitantly with rabeprazole tablets.

In clinical trials, antacids were used concomitantly with the administration of rabeprazole tablets and, in a specific study designed to define this interaction, no interaction with liquid antacids was observed. There was no clinically relevant interaction with food.

In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolized by isoenzymes of CYP450 (CYP2C19 and CYP3A4). In these studies, at expected human plasma concentrations rabeprazole neither induces nor inhibits CYP3A4; and although in *vitro* studies may not always be predictive of *in vivo* status these findings indicate that no interaction is expected between rabeprazole and cyclosporine.

Co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg once daily) to healthy volunteers resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Although co-administration with rabeprazole was not studied, similar results are expected with other proton pump inhibitors. Therefore PPIs, including rabeprazole, should not be coadminislered with atazanavir.

Gastric acid antisecretory effect of Rabeprazole Tablets may increase intragastric pH and reduce solubility of rilpivirine hydrochloride, resulting in a decrease in the blood concentration of rilpivirine hydrochloride.

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) 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 (see section 4.4)

4.6 Pregnancy and Lactation
Pregnancy
There are no data on the safety of rabeprazole in human pregnancy. 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. Rabeprazole tablets 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 rabeprazole should not be used during breast feeding.

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 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 most commonly reported adverse drug reactions, during controlled clinical trials with rabeprazole were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth. The majority of adverse events experienced during clinical studies were mild or moderate in severity, and transient in nature.

The following adverse events have been reported from clinical trial and post-marketed experience.

Frequencies are defined as: common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
Infections and infestations		Infection				
Blood and the lymphatic system disorders				Neutropenia Leucopenia Thrombocytop-enia Leucocytosis		
Cardiovascular disorders	Increase in blood pressure	Palpitations				
Immune system disorders				Hypersensitivity [1,2]		Systemic lupus erythematosus [4]
Metabolism and nutrition disorders				Anorexia Hypomagnesemia		Hyponatremia Hypomagnesaemia [4]
Psychiatric disorders		Insomnia	Nervousness	Depression		Confusion
Nervous system disorders		Headache Dizziness	Somnolence			
Eye disorders				Visual disturbance Blurred vision		
Vascular disorders						Peripheral oedema
Respiratory, thoracic and mediastinal disorders		Cough Pharyngitis Rhinitis	Bronchitis Sinusitis			
Gastrointestinal disorders	Stomatitis	Diarrhoea Vomiting Nausea Abdominal pain Constipation Flatulence Fundic gland polyps (benign)	Dyspepsia Dry mouth Eructation	Gastritis Taste disturbance		

Hepato-biliary disorders				Hepatitis Jaundice Hepatic encepha-lopathy[3]		
Skin and subcutane-ous tissue disorders			Rash Erythema[2]	Pruritus Sweating Bullous reac-tions[2]	Erythema multiforme, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS)	Cutane-ous lupus erythema-tosus[4]
Musculo-skeletal, connective tissue and bone disorders		Non-specific pain Back pain	Myalgia Leg cramps Arthralgia Fracture of the hip, wrist or spine[4]			
Renal and urinary disorders			Urinary tract infec-tion	Interstitial nephritis		Acute kidney injury
Repro-ductive system and breast disorders						Gynaeco-mastia
General disorders and administra-tion site conditions		Asthenia Influenza like ill-ness	Chest pain Chills Pyrexia			
Investiga-tions		Increased hepatic enzymes[3]	Weight increased			

1 Includes facial swelling, hypotension and dyspnoea.
2 Erythema, bullous reactions and hypersensitivity reactions have usually resolved after discontinuation of therapy.
3 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 rabeprazole is first initiated in such patients (see section 4.4).
4 See Special Warnings and Precautions for Use (section 4.4)

Pneumonia and TSH elevations have been reported from worldwide marketing experience with rabeprazole sodium.

4.9 Overdose

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60mg twice daily, or 160mg once daily. Effects are generally minimal, representative of the known adverse event profile and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is, therefore, not readily dialyzable. 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 H_2 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.

Anti-secretory Activity: After oral administration of a 20 mg dose of rabeprazole sodium the onset of the anti-secretory effect occurs within one hour, with the maximum effect occurring within two to four hours Inhibition of basal and food stimulated acid secretion 23 hours after the first dose of sodium rabeprazole are 69% and 82% respectively and the duration or inhibition lasts up to 48 hours. The inhibitory effect of sodium rabeprazole on acid secretion increases slightly with repeated once-daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity normalizes over 2 to 3 days.

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

Intragastric pH Effects: Administration of rabeprazole sodium at 5, 10 and 20 mg once a day all resulted in a significantly increased intragastric pH in healthy adult men. The proportion of time that showed a pH of 4 or above in the period of 24 hours on day 5 of administration was 46% and 63% for EM and PM at 5 mg once a day, respectively, 58% and 72% for EM and PM at 10 mg once a day, respectively, and 61% and 76% for EM and PM at 20 mg once a day, respectively (see section 5.2).

Serum Gastrin Effects: In clinical studies patients were treated once daily with 10 or 20 mg rabeprazole sodium, for up to 43 months duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion and remained stable while treatment was continued. Gastrin values returned to pre-treatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

Human gastric biopsy specimens from the antrum and the fundus from over 500 patients receiving rabeprazole or comparator treatment for up to 8 weeks have not detected changes in ECL cell histology, degree of gastritis, incidence of atrophic gastritis, intestinal metaplasia or distribution of *H. pylori* infection. In over 250 patients followed tor 36 months or continuous therapy, no significant change in findings present at baseline was observed.

Other Effects: Systemic effects of rabeprazole sodium in the CNS, cardiovascular and respiratory systems have not been found to date. Rabeprazole sodium, given in oral doses of 20 mg for 2 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, estrogen, testosterone, prolactin, cholecystokinin, secretin, glucagon, follicle stimulating hormone (FSH), luteinizing hormone (LH), renin, aldosterone or somatotrophic hormone.

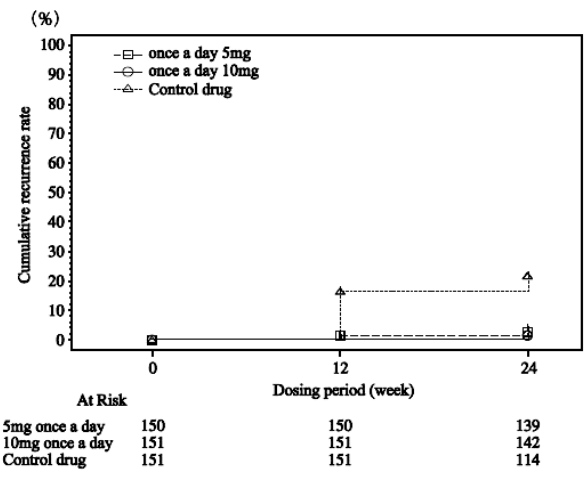
Clinical Efficacy

Prevention of gastric and duodenal ulcer recurrences associated with low-dose aspirin therapy (Study 308).

The table below shows cumulative rates of recurrence for gastric and duodenal ulcer at 24 weeks after administration estimated using the Kaplan-Meier method in a double-blind comparative study involving patients requiring long-term treatment with low-dose aspirin (at 81 mg or 100 mg/day) with a past history of gastric ulcer or duodenal ulcer.

	5 mg once a day (150 patients)	10 mg once a day (151 patients)	Control drug [c] (151 patients)
Number of patients with recurrences	4	2	32
Cumulative recurrence rate at 24 weeks after administration [a] (95% confidence interval)	2.8% (1.04, 7.17)	1.4% (0.35, 5.51)	21.7% (15.84, 29.27)
Hazard ratio against control drug (95% confidence interval)	0.11 (0.04, 0.31)	0.05 (0.01, 0.23)	-
P-value [b]	**P**< 0.001	**P**< 0.001	-

[a] Estimated using the Kaplan-Meier method
[b] Based on the log-ranktest
[c] Teprenone (50 mg 3 times a day)



Cumulative rates of recurrence for gastric ulcer or duo-denal ulcer based on Kaplan-Meier method

5.2 Pharmacokinetic Properties

Absorption: Rabeprazole 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. Absorption is rapid, with peak plasma levels of rabeprazole occurring approximately 35 hours after a 20 mg dose Peak plasma concentrations (C_{max} of rabeprazole and AUC are linear over the dose range or 10mg 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 ml/min. Neither food nor the time of day of administration or the treatment affect the absorption of rabeprazole sodium.

The pharmacokinetic parameters of rabeprazole sodium (on day 5 of administration) administered repeatedly to healthy adult men in a fasting state at 5, 10 and 20 mg are shown below.

Pharmacokinetic parameters of rabeprazole sodium in plasma when repeatedly administered (at 5 mg, 10 mg and 20 mg) to healthy adult men

Dose	Phenotype	C_{max} (ng/mL)	t_{max} (hr)	AUC (0-t) (ng.hr/mL)	$t_{½}$ (hr)
5mg	EM*	146 ± 56	3.0 (2.0-4.5)	236 ± 97	1.8 ± 0.9
	PM*	252 ± 55	2.5 (1.5-5.5)	585 ± 137	4.2 ± 0.5
10mg	EM*	383 ± 83	3.3 (2.0-5.0)	539 ± 200	1.5 ± 0.4
	PM*	509 ± 64	2.8 (2.0-4.5)	1230 ± 200	3.8 ± 0.3
20mg	EM*	654 ± 348	4.0 (2.5-8.0)	994 ± 477	2.3 ± 1.4
	PM*	822 ± 232	3.3 (3.0-6.0)	2331 ± 663	3.7 ± 0.3

Values under each item are shown as mean ± standard deviation, except for t_{max}, which is shown as median (minimum value-maximum value).
EM, n=16; PM, n=8
*The phenotype of cytochrome P450 2C19 (CYP2C19), a hepatic metabolizing enzyme, is classified based on genotype as below.
EM (extensive metabolizer): CYP2C19*1/*1, CYP2C19*1/*2 or CYP2C19*1/*3
PM (poor metabolizer): CYP2C19*2/*2, CYP2C19*2/*3 or CYP2C19*3/*3

Distribution: 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.

Following a single 20 mg ^{14}C labeled oral dose of sodium rabeprazole, no unchanged drug was excreted in the urine. Approximately 90% or 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: Adjusted for body mass and height, there are no significant gender differences in pharmacokinetic parameters following a single 20 mg dose of rabeprazole.

Renal dysfunction: In patients with stable, end-stage, renal failure requiring maintenance hemodialysis (creatinine clearance ≤5ml/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: Following a single 20mg 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 pharmacodynamics response (gastric pH control) in the two groups was clinically comparable.

Elderly: Elimination of rabeprazole was somewhat decreased in the elderly. Following 7 days of daily dosing with 20mg of rabeprazole sodium, the AUG approximately doubled, the C_{max} increased by 60% and $t_{1/2}$ increased by approximately 30% as compared to young healthy volunteers. However, there was no evidence of rabeprazole accumulation.

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

5.3 Pre-clinical Safety Data

Pre-clinical effects were observed only at exposures sufficiently in excess of the maximum human exposure that make concerns for human safety negligible in respect of animal data.
Studies on mutagenicity gave equivocal results. Tests in mouse lymphoma cell line were positive, but in vivo micronucleus and in vivo and in vitro DNA repair tests were negative. Carcinogenicity studies revealed no special hazard for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 Product description

10mg: Pink, coated, elliptical, biconvex tablet.
20mg: Yellow, coated, elliptical, biconvex tablet.

6.2 List of Excipients

Povidone, Low subst. hydroxypropyl cellulose, Magnesium oxide, Mannitol, Magnesium Stearate, Ethyl cellulose, Methacrylic acid-ethyl acrylate copolymer 30% dispersion, Propylene glycol, Iron oxide yellow (E 172), Titanium dioxide (E 171), Talc, Iron oxide red (172) [10mg only]

Methacrylic acid-ethyl acrylate copolymer 30% dispersion contains:
Methacrylic acid-ethyl acrylate co- polymer (1:1), Polysorbate 80, Sodium lauryl sulphate.

6.3 Incompatibilities

None.

6.4 Shelf-life

24 months.

6.5 Special precautions for storage

Store below 25°C. Store in the original package in order to protect from moisture.

6.6 Nature and Contents of Container

Rabeprazole tablets 10mg- Pack of 14 tablets
Rabeprazole tablets 20mg- Pack of 14 tablets

6.7 Instructions for Use/Handling

No specified instruction needed.

7. MANUFACTURER

BALKANPHARMA-DUPNITSA AD
3 Samokovsko Shosse Str.,
Dupnitsa 2600, Bulgaria

Date of revision of the text:
11-2021