PARIT*
Rabeprazole Tablets IP

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each enteric coated tablet contains:
Rabeprazole Sodium IP 20 mg
Colours: Ferric Oxide USPNF (yellow) and Titanium Dioxide IP

PHARMACEUTICAL FORM

Enteric-coated tablets

CLINICAL PARTICULARS

Therapeutic Indications

*PARIT* tablets are indicated for the treatment of:

- Gastro-Esophageal Reflux Disease (GERD) including:
  - Erosive or Ulcerative Gastro-Esophageal Reflux Disease (GERD)
  - Gastro-Esophageal Reflux Disease (GERD) Maintenance
  - Symptomatic Gastroesophageal Reflux Disease (symptomatic GERD)
- Active Duodenal Ulcer
- Zollinger-Ellison Syndrome

Posology and Method of Administration

General

Time of day was not shown to have any significant effect on rabeprazole sodium activity.

Adults

Erosive or Ulcerative Gastro-Esophageal Reflux Disease (GERD):

Dose: The recommended oral dose for this condition is *PARIT* 20 mg once daily.
Duration: This dose should be taken for 4 to 8 weeks. For those patients who have not healed after eight weeks of treatment, an additional 8 week course may be considered.

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

Dose: The recommended oral dose for this condition is *PARIT* 20 mg once daily.
Duration: The duration of treatment is adjusted according to clinical need.
**Symptomatic Gastro-Esophageal Reflux Disease (symptomatic GERD)**

Dose: The recommended oral dose for this condition is PARIT 20 mg once daily. Duration: If symptom control has not been achieved during 4 weeks, the patient should be further investigated.

**Active Duodenal Ulcer:**

Dose: The recommended oral dose for active duodenal ulcer is PARIT 20 mg once daily. Duration: Most patients with active duodenal ulcer heal within 2 to 4 weeks. However, a few patients may require an additional four weeks of therapy to achieve healing.

**Zollinger-Ellison Syndrome:**

Dose: The dose necessary 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. Duration: Dosing should continue for as long as clinically necessary. Some patients with Zollinger-Ellison Syndrome have been treated continuously with rabeprazole for up to 1 year.

**Children and Adolescents**

Safety and effectiveness of rabeprazole sodium 20 mg for the short-term (up to 8 weeks) treatment of GERD in adolescents 12 years of age and above is supported by a) extrapolation of results from adequate and well-controlled studies that supported the effectiveness of rabeprazole sodium for adults; b) safety and pharmacokinetic studies performed in adolescent patients. The recommended oral dose for adolescents 12 years of age and above is 20 mg once daily for up to 8 weeks.

The safety and effectiveness of rabeprazole sodium for other uses have not been established in pediatric patients.

**Renal Impairment:**

No dosage adjustment is necessary for patients with renal impairment.

**Hepatic Impairment**

Patients with mild to moderate hepatic impairment experience higher exposure to rabeprazole sodium at a given dose than do healthy patients.

Caution should be exercised in patients with severe hepatic impairment who are co-administered with rabeprazole.

**Elderly**

No dosage adjustment is necessary for the elderly
Contraindications

Rabeprazole is contraindicated in patients with known hypersensitivity to rabeprazole sodium, substituted benzimidazoles or to any excipient used in the formulation.

Special Warnings and Special Precautions for Use

Pre-Existing Malignancy

Symptomatic response to therapy with rabeprazole sodium does not preclude the presence of gastric malignancy.

Swallow as Tablet

Patients should be cautioned that rabeprazole sodium tablets should not be chewed or crushed but should be swallowed whole.

Patients with Severe Hepatic Dysfunction

Although 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 following administration of 20 mg tablets, the prescriber is advised to exercise caution when treatment with rabeprazole sodium is first initiated in patients with severe hepatic dysfunction. The exposure to rabeprazole sodium (AUC) following administration of 20 mg tablets in patients with significant hepatic dysfunction is approximately two-fold that of healthy patients.

Hypomagnesaemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with proton pump inhibitors (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.

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 [see Undesirable Effects].

Fractures

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, and long-term PPI therapy (a year or longer).
Concomitant use of Rabeprazole with Methotrexate

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.

Clostridium difficile

Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as *Clostridium difficile*.

Interaction with Other Medicaments and Other Forms of Interaction

Cytochrome P450 System

Rabeprazole sodium, as is 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. Specifically, *in vitro* studies with human liver microsomes indicated that rabeprazole sodium is metabolized by isoenzymes CYP2C19 and CYP3A4.

Studies in healthy subjects have shown that rabeprazole sodium tablets does not have pharmacokinetic or clinically significant interactions with warfarin, phenytoin, theophylline or diazepam (regardless of whether the subject was an extensive or poor diazepam metabolizer), each of which is metabolized by the CYP450 system.

Combination therapy with antimicrobials - 16 healthy volunteers were given 20 mg rabeprazole sodium, 1000 mg amoxicillin, 500 mg clarithromycin, or the combination of all 3 rabeprazole, amoxicillin, and clarithromycin (RAC) in a four way crossover study. The AUC and $C_{\text{max}}$ for clarithromycin and amoxicillin were similar during combined treatment compared to monotherapy. The rabeprazole AUC and $C_{\text{max}}$ increased by 11% and 34% and the 14-hydroxyclarithromycin (active metabolite of clarithromycin) AUC and $C_{\text{max}}$ increased by 42% and 46% during the combined treatment compared to values obtained during monotherapy. This increase in exposure to rabeprazole and the 14-hydroxyclarithromycin is not considered to be clinically significant.

Interactions due to Inhibition of Gastric Acid Secretion

Rabeprazole sodium produces a profound and long lasting inhibition of gastric acid secretion. An interaction with compounds whose absorption is pH-dependent may occur. Specifically, co-administration of rabeprazole sodium results in an approximate 30% 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 digoxin, ketoconazole or other drugs whose absorption is pH-dependent are taken concomitantly with rabeprazole sodium.
**Atazanavir**

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 co-administered with atazanavir.

**Antacids**

In clinical trials, antacids were used concomitantly with rabeprazole sodium where required and, in a specific pharmacokinetic study designed to define this interaction, no clinically significant interaction with aluminium hydroxide gel or magnesium hydroxide was observed.

**Food**

In adults, no clinically relevant interaction with food was observed in a Japanese clinical study using a low-fat meal. Administration of rabeprazole sodium delayed release tablets with a high fat meal may delay its absorption up to 4 hours or longer; however, the C\text{max} and the extent of absorption (AUC) are not altered.

**Cyclosporin**

*In vitro* incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporin metabolism with an IC\textsubscript{50} of 62 micromolar, a concentration that is over 50 times higher than the C\text{max} in healthy volunteers following 14 days dosing with 20 mg of rabeprazole. This degree of inhibition is similar to that by omeprazole at equivalent concentrations.

**Methotrexate**

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.

**Clopidogrel**

Concomitant administration of rabeprazole and clopidogrel in healthy subjects had no clinically meaningful effect on exposure to the active metabolite of clopidogrel. No dose adjustment of clopidogrel is necessary when administered with an approved dose of rabeprazole.

**Pregnancy and Lactation**

**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 feto-placental transfer occurs in rats.

There are no adequate or well-controlled studies in pregnant women and post-marketing experience is very limited. Rabeprazole sodium should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Lactation**

It is not known whether rabeprazole sodium is excreted in human breast milk and there are no studies in lactating women. Rabeprazole sodium is however excreted in rat mammary secretions. Therefore, rabeprazole sodium should not be administered to nursing mothers. If rabeprazole sodium administration is indispensable, nursing should be discontinued.

**Effects on Ability to Drive and Use Machines**

If alertness is impaired due to somnolence, it is recommended that driving and operating complex machinery be avoided, however, based on its pharmacodynamic properties and adverse event profile in clinical trials, it is unlikely that rabeprazole sodium would cause impairment of driving performance or compromise the ability to use machinery.

**Undesirable Effects**

Rabeprazole sodium tablets were generally well tolerated during clinical trials of adults and adolescents. The observed adverse events have generally been mild/moderate and transient in nature and consistent between adults and adolescents.

The table below contains a subset of adverse events reported in placebo-controlled North American clinical trials in adults. Data is broken down to show both total numbers of the listed ADE’s reported as treatment-emergent signs and symptoms (TESS) and to show the number of reports considered possibly or probably related to study drug treatment by the reporter.

**Table I. Adverse Events Reported in Placebo-controlled North American Clinical Trials with Rabeprazole Delayed Release Tablets**

<table>
<thead>
<tr>
<th>BODY SYSTEM</th>
<th>Total Reported TESS</th>
<th>TESS considered Possibly or Probably Related to Study Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rabeprazole n=749</td>
<td>Placebo n=89</td>
</tr>
<tr>
<td></td>
<td>Rabeprazole n=749</td>
<td>Placebo n=89</td>
</tr>
<tr>
<td>WHOLE BODY Headache</td>
<td>96 (13%)</td>
<td>9 (10%)</td>
</tr>
<tr>
<td></td>
<td>22 (3%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>GASTROINTESTINAL</td>
<td>39 (5%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>77 (10%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td></td>
<td>6 (1%)</td>
<td>20 (3%)</td>
</tr>
<tr>
<td></td>
<td>1 (1%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36 (5%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td></td>
<td>6 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>4 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>15 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td>4 (1%)</td>
</tr>
</tbody>
</table>
**Post-Marketing Experience**

There have been reports of hepatic enzyme increase, and rarely reports of hepatitis and jaundice. Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis. There have also been rare reports of hypomagnesemia, thrombocytopenia, neutropenia, leukopenia, bullous or urticarial skin eruptions, acute systemic allergic reactions, myalgia and arthralgia. There have been very rare reports of interstitial nephritis, gynaecomastia, erythema multiforme, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome.

There has been no other notable abnormality in laboratory values attributable to treatment with rabeprazole sodium.

There have been post-marketing reports of bone fractures (see Special Warnings and Special Precautions for Use).

**Overdose**

**Animal Study Data**

LD$_{50}$ of rabeprazole sodium after single oral administration is > 1,000 mg/kg in mice, > 1,300 mg/kg in rats. The lethal dose of rabeprazole sodium after single oral administration is > 2,000 mg/kg in dogs (approximately 2,500 to 5,000 times the recommended human dose, i.e., 20 mg/day), and is > 200 mg/kg in mice and > 150 mg/kg in rats, by single intravenous injection. Peak plasma levels in animals are 8 to 37 times the human peak concentration (C$_{\text{max}}$=427 ng/mL) after the first oral dose of 100 mg/kg in mice, 300 mg/kg in rats and 25 mg/kg in dogs.

**Symptoms of Overdosage**

Experience with deliberate or accidental overdose is limited. There has been no experience with large overdoses with rabeprazole. A few reports of accidental overdosage with rabeprazole delayed release tablets have been received. There were no clinical signs or symptoms associated with any reported overdose. Patients with Zollinger-Ellison syndrome have been treated with up to 180 mg rabeprazole delayed release tablets daily. No specific antidote for rabeprazole is known. Rabeprazole is extensively protein bound and is not readily dialysable. In the event of overdosage, treatment should be symptomatic and supportive.

**Treatment**

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.
PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

**Pharmacotherapeutic group**

Alimentary tract and metabolism, Drugs for peptic ulcer and gastro-esophageal reflux disease (GERD), proton pump inhibitors.

ATC code: A02B C04

**Mechanism of Action**

Rabeprazole sodium belongs to the class of anti-secretory compounds, the substituted benzimidazoles.

Rabeprazole sodium suppresses gastric acid secretion by the specific inhibition of the H⁺/K⁺-ATPase enzyme at the secretory surface of the gastric parietal cell. This enzyme system is regarded as the acid (proton) pump, and therefore rabeprazole sodium is classified as a gastric proton-pump inhibitor, blocking the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus.

Rabeprazole sodium does not exhibit anticholinergic properties.

**Anti-Secretory Activity**

After oral administration of a 20 mg dose of rabeprazole sodium delayed release tablets, the onset of the anti-secretory effect occurs within one hour. Inhibition of basal and food stimulated acid secretion 23 hours after the first dose of rabeprazole sodium are 69% and 82% respectively and the duration of inhibition lasts up to 48 hours. This duration of pharmacodynamic action is much longer than the pharmacokinetic half life (approximately one hour) would predict. This effect is probably due to the prolonged binding to the parietal H⁺/K⁺-ATPase enzyme. The inhibitory effect of rabeprazole sodium on acid secretion increases slightly with repeated once-daily dosing, achieving steady state inhibition after three days. When the drug is discontinued, secretory activity begins to normalize over 1 to 2 days.

**Serum Gastrin Effects**

In clinical studies patients were treated once daily with 10 or 20 mg rabeprazole sodium delayed release tablets, for up to 5 years duration. Serum gastrin levels increased during the first 2 to 8 weeks reflecting the inhibitory effects on acid secretion.

**Enterochromaffin-like (ECL) Cell Effects**

Rats

Gastric carcinoid tumors were observed in one of two 24 month carcinogenicity studies in rats but not in a similar study in mice. Gastric neuroendocrine cell
hyperplasia and gastric carcinoid tumors were recorded in female rats at all dose levels. Minimal neuroendocrine cell hyperplasia but no gastric carcinoid tumors were recorded in male rats. Hypergastrinemia secondary to prolonged and sustained hypochlorhydria has been proposed to be the mechanism by which neuroendocrine cell hyperplasia develops.

**Human**

Human gastric biopsy specimens from the antrum and the fundus from over 500 patients receiving rabeprazole sodium delayed release tablets or comparator treatment for up to 8 weeks detected no consistent changes in ECL cell histology, degree of gastritis, incidence of atrophic gastritis, intestinal metaplasia or distribution of *H. pylori* infection.

In over 400 patients treated with rabeprazole sodium delayed release (10 or 20 mg/day) for up to one year, the incidence of ECL hyperplasia was low and comparable to that observed with omeprazole (20 mg/day); no patient demonstrated the adenomatoid changes or carcinoid tumors as observed in rats.

**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, glucagon, follicle stimulating hormone (FSH), luteinising hormone (LH), renin, aldosterone, or somatotrophic hormone.

**Pharmacokinetic Properties**

**Absorption**

Rabeprazole sodium is presented as an enteric-coated tablet. This presentation is necessary because rabeprazole sodium is acid-labile. Absorption of rabeprazole sodium therefore begins only after the tablet leaves the stomach. Absorption is rapid, with peak plasma levels of rabeprazole sodium occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (C\text{max}) of rabeprazole sodium 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%. 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 3.8 ml/min/kg. In patients with chronic hepatic disease, the AUC doubled compared to healthy volunteers, reflecting a decreased first-pass effect, and the plasma half-life increased 2-3 fold. Neither time of day of administration nor antacids significantly affect the absorption of rabeprazole sodium. Administration of rabeprazole sodium with a high fat meal may delay its absorption up to 4 hours or longer; however, the C\text{max} and the extent of absorption (AUC) are not altered.
**Distribution**

Rabeprazole sodium is approximately 97% bound to human plasma proteins.

**Metabolism and Excretion**

**Healthy Humans**
Following a single 20 mg $^{14}$C labeled oral dose of rabeprazole sodium delayed release tablets, 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 also found in the species used in the toxicology studies. The remainder of the dose was recovered in faeces. Total recovery was 99.8%. This implies a low biliary secretion of the metabolites of rabeprazole sodium. The thioether (M1) is the main metabolite. The desmethyl metabolite (M3), the only active metabolite, has only been observed at low levels and in a single subject after 80 mg of rabeprazole sodium.

**End-Stage Renal Failure**
In patients with stable, end-stage, renal failure requiring maintenance hemodialysis (creatinine clearance <5ml/min/1.73m$^2$), the disposition of rabeprazole sodium delayed release was very similar to that in healthy volunteers.

**Chronic Compensated Cirrhosis**
Patients with chronic compensated cirrhosis have tolerated rabeprazole sodium delayed release 20 mg daily, although the AUC approximately doubled and the $C_{\text{max}}$ increased by 50% compared to healthy sex-matched subjects.

**Elderly**
Elimination of rabeprazole sodium was somewhat decreased in the elderly. Following 7 days of daily dosing with 20 mg of rabeprazole sodium delayed release, the AUC approximately doubled, the $C_{\text{max}}$ increased by 60% as compared to young healthy volunteers. However there was no evidence of rabeprazole sodium accumulation.

**Pediatric Patients 12 to 16 Years of Age**

The pharmacokinetics of rabeprazole was studied in 12 adolescent patients with GERD 12 to 16 years of age, in a multicenter study. Patients received rabeprazole 20 mg tablets once daily for 5 or 7 days. An approximate 40% increase in 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 volunteers.

**CYP2C19 Polymorphism**
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 $C_{\text{max}}$ had increased by only 40%.

**Preclinical Safety Data**
General

The major non-neoplastic changes were confined to the stomach including mucosal thickening, eosinophilic chief cells, hyperplastic gastropathy, and neuroendocrine cell hyperplasia in the fundic mucosa. These changes were generally dose-related in incidence and consistent with the expected pharmacological, antisecretory and hypergastrinemic effects of chronic treatment.

Mutagenicity

Rabeprazole was not genotoxic in the in vitro test for chromosome aberration in CHL/IU cells, the in vivo mouse micronucleus test, and in the in vivo/ex vivo and in vitro unscheduled DNA synthesis assays in rat hepatocytes. The CHO/HGPRT forward gene mutation assay gave a borderline result. The Ames test gave positive and negative results in repeat assays and the L5178Y tk mouse lymphoma assay was positive at $\geq 25 \, \mu g/mL$ and negative at $20 \, \mu g/mL$ (27 times the human $C_{\text{max}}$ based on mg/m²).

Carcinogenicity

CD-1 Mice
Carcinogenicity studies conducted with rabeprazole sodium in CD-1 mice (22-24 months) given daily oral doses of 2, 20 and 200 mg/kg (highest dose reduced to 100 mg/kg at week 41 due to high mortality) showed no evidence of treatment-related carcinogenicity.

Fischer-344 Rats
Carcinogenicity studies conducted in Fischer-344 rats (24 months) given daily oral doses of 2, 6 and 20 mg/kg showed no evidence of treatment-related carcinogenicity, but diffuse and/or nodular hyperplasia of neuroendocrine cells was recorded in treated males and females.

Sprague-Dawley Rats
In a 24 months carcinogenicity study, male and female Sprague-Dawley rats were given daily oral doses of 5, 15, 30 and 60 mg/kg and 5, 15, 30, 60 and 120 mg/kg respectively. In this study gastric carcinoid tumors were observed at all dose levels in female but not in male rats. Additionally, neuroendocrine cell hyperplasia was recorded at all doses in females but rarely observed at the two highest doses in male rats.

p53 (+/-) Mice
In a 28 week p53 (+/-) heterozygous mouse study, mice were given daily oral doses of 20, 60 or 200 mg/kg per day. There were no indications of carcinogenic response in the p53 (+/-) heterozygous mice.

Fertility

Investigation of the reproductive performance of rats and the reproductive development of the progeny in a two generation perinatal/postnatal study showed that daily intravenous doses of up to 30 mg/kg produced no adverse effects on the fertility and general reproduction of parental animals or their offspring.
**Juvenile Animal Studies**

In juvenile animal studies (5, 25, and 150 mg/kg for a 5-Week Oral Toxicity Study in the Juvenile Rat with a 13-Week Recovery Period, and 3 10 or 30 mg/kg/day for a 13-Week Oral Toxicity Study in the Juvenile Dog with by a 13-Week Recovery Period) observations 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 completely reversible over the 13-week recovery periods. Although body weights and/or crown-rump lengths were minimally decreased during dosing, no effects on the developmental parameters were noted in either juvenile rats or dogs.

**PHARMACEUTICAL PARTICULARS**

**List of Excipients**

Mannitol, Light Magnesium Oxide, Low-substituted Hydroxypropyl Cellulose (L-HPC-LH21), Isopropyl alcohol, Hydroxypropylcellulose (HPC-L), Magnesium stearate, Ethylcellulose (Ethocel-10), Hypromellose Phthalate, Myvacet 9-45 K (Glycerol Esters of Fatty Acids), Talc, Titanium dioxide, Ferric oxide (yellow), Opacode Brown S-1-16507 (Tablet Printing Ink), n-Butanol.

**Incompatibilities**

None known

**Shelf Life**

12 months

The expiry date is indicated on the label and packaging.

**Special Precautions for Storage**

Store below 25°C protected from light and moisture

Keep out of reach of children.

**Nature and Specification of Container**

Aluminium/aluminium blister strips

**Instructions for Use/ Handling**

There are no special requirements for use or handling of this product

For further information please contact: