SCOTT-EDIL
Enhancing Life

SCOTT-EDIL PHARMACIA LTD.

56, E.P.I.P Phase –I, Jharmajri, Baddi, Distt. Solan-173205 (HP) , India

Summary of Product Characteristics (SPC)

1. Name of the medicinal product

Rabikol ® (Rabeprazole Sodium & Domperidone Sustained Release Capsules)

1.1 ***International Non-Proprietary Name (INN)***
Rabeprazole Sodium & Domperidone Sustained Release Capsules

1.2 ***Strength***

20/30 mg

1.3 ***Pharmaceutical form***
Oral Solid Dosage Form
Visual Description: Maroon coloured cap and Light yellow coloured body, hard gelatin capsule of size '2" containing Brown & Orange coloured spherical enteric coated Pellets.

2. Qualitative and quantitative composition

Each hard gelatin capsule contains
Rabeprazole Sodium BP 20 mg
(as enteric coated pellets)
Domperidone BP 30 mg
(as sustained release pellets)
Approved colour used in empty shells & pellets

3. Pharmaceutical form

Capsule for oral use.

4. Clinical particulars

4.1 Therapeutic indications
Rabikol® Capsule is highly indicated for the cure or relief of symptoms of:
- Active Duodenal ulcer
- Active benign gastric ulcer
- Symptomatic erosive or ulcerative GERD
- Long-term management of GERD
- Dyspepsia
- Nausea associated with acid peptic disorders
- Post-operative nausea and vomiting
- Chronic gastritis / Peptic Ulcer disease
- Zollinger Ellision Syndrome

4.2 Posology and method of administration

Posology

One capsule once daily

Method of administration

Rabikol® should be swallowed with a glass of water.

4.3 Contraindications

Rabeprazole & Domperidone sustained release capsules are contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles, domperidone or to any component of the formulation. It should not be used whenever stimulation of gastric motility is to be avoided or could be harmf ul,e.g. in the presence of gastro-intestinal hemorrhage, obstruction or perforation. It is also contra-indicated in patients with a prolactin-releasing pituitary tumor (prolactinoma).

4.4 Special warnings and precautions for use

Eliminate the possibility of malignancy if gastric ulcer is suspected before initiating treatment with Rabeprazole and all PPIs as they may mask symptoms and delay diagnosis. Monitor patients on warfaring or phenytoin therapy, reduce dose if necessary. Domperidone can cause a rise in serum prolactin level resulting in galactorrhea in females and less frequently gynaecomastia in males. Hypertensive crisis may occur in patients with phaeochomocytonia, renal impairment or those at risk of fluid retentions. Use with cause in established case of osteoporosis-related fractures.

Renal Impairement: Adjust the dose according to severity of imparment.

Hepatic impairment: Do not use at all. Domperidone is principally metabolized by the liver.

Pregnancy: Use only if the drug is needed

Lactation: Breastfeeding is not recommended for nursing mothers on RABIKOL

Pediatic use: Not recommended

4.5 Interaction with other medicinal products and other forms of interaction

Rabeprazole

Rabeprazole is metabolized by the cytochrome P450 (CYP450) drug metabolizing enzyme system. Rabeprazole does not have clinically significant interactions with other drugs metabolized by the CYP450 system, such as warfarin, theophylline, diazepam and phenytoin. Rabeprazole produces sustained inhibition of gastric acid secretion. An interaction with compounds which are dependent on gastric pH for absorption like ketoconazole may occur due to the magnitude of acid suppression observed with rabeprazole. Therefore, patients may need to be monitored when such drugs are taken concomitantly with rabeprazole. Co-administration of rabeprazole and antacids produced no clinically relevant changes in plasma rabeprazole concentrations.

Domperidone

The main metabolic pathway of domperidone is through CYP3A4. In vitro data suggest that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone. In vivo interaction studies with ketoconazole revealed a marked inhibition of domperidone CYP3A4 mediated first pass metabolism by ketoconazole. A pharmacokinetic study has demonstrated that the AUC and the peak plasma concentration of domperidone is increased by a factor of 3 when oral ketoconazole is administered concomitantly (at steady state). A slight QT-prolonging effect (mean less than 10msec) of this combination was detected, which was greater than the one seen with ketoconazole alone. A QT prolonging effect could not be detected when domperidone was given alone in patients with no co-morbidity, even at high oral doses (up to 160mg/day). The results of this interaction study should be taken into account when prescribing domperidone concomitantly with strong CYP3A4 inhibitors: for example: ketoconazole, ritonavir and erythromycin. While adverse interactions have not been reported in general clinical use, domperidone has the potential to interact with dopamine agonist (e.g. bromocriptine), antimuscarinic and opioid analgesics. It may also enhance the absorption of concomitantly administered drugs especially in cases of delayed gastric emptying.

4.6 Pregnancy and lactation

<u>Pregnancy</u>

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 foetus due to rabeprazole sodium, although low foeto-placental transfer occurs in rats. Rabeprazole is contraindicated during pregnancy.

There are limited post-marketing data on the use of domperidone in pregnant women. A study in rats has shown reproductive toxicity at a high, maternally toxic dose. The potential risk for humans is unknown. Therefore, domperidone should only be used during pregnancy when justified by the anticipated therapeutic benefit.

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 must not be used during breast feeding.

Domperidone is excreted in human milk and breast-fed infants receive less than 0.1% of the maternal weight-adjusted dose. Occurrence of adverse effects, in particular cardiac effects cannot be excluded after exposure via breast milk. A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from domperidone therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the women. Caution should be exercised in case of QTc prolongation risk factor in breast-fed infants.

Paediatric Use

Rabeprazole is not recommended for use in children due to a lack of data on safety and efficacy.

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.

Domperidone has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Adverse effects with rabeprazole are mild to moderate in intensity and included malaise, diarrhea, nausea, skin eruptions, headache and dizziness. Abnormal laboratory findings (increased hepatic enzymes, LDH, blood urea nitrogen) observed with rabeprazole were similar in incidence and severity with comparator agents and reversible with cessation of therapy.

Domperidone has been found to be associated with increased serum prolactin, which may be associated with galactorrhea, less frequently gynaecomastia, breast enlargement and soreness. Reduced libido has been reported. Occasional rashes and other allergenic phenomena are also reported. Domperidone does not readily cross the normally functioning blood brain barrier and is therefore less likely to interfere with the central dopaminergic function. However, acute extrapyramidal dystonic reactions have been reported with domperidone.

4.9 Overdose
Rabeprazole

There has been no experience with large overdoses with rabeprazole. In the event of over dosage, treatment should be symptomatic and supportive.

Domperidone

Symptoms of over dosage may include drowsiness, disorientation and extrapyramidal reactions, especially in children.

Treatment

There is no specific antidote to domperidone, but in the event of overdose, gastric lavage as well as the administration of activated charcoal, may be useful. Close medical supervision and supportive therapy is recommended. Anticholinergic, anti-Parkinson drugs may be helpful in controlling extrapyramidal reactions.

5. Pharmacological properties

Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazoles proton-pump inhibitors) that do not exhibit anticholinergic or histamine H2 —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.

Domperidone is a derivative of benzimidazoles that possesses both prokinetic and antiemetic properties due to its inhibitory action at dopamine D2 receptors.

5.1 Pharmacodynamic properties
Rabeprazole

Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazoles proton-pump inhibitors) that do not exhibit anticholinergic or histamine H2-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 sulfonamide. 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.

Antisecretory Activity

The antisecretory effect begins within one hour after oral administration of 20 mg rabeprazole. The median inhibitory effect of rabeprazole on 24 hour gastric acidity is 88% of maximal after the first dose. Rabeprazole 20 mg 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 (1-2 hours) reflects the sustained inactivation of the H+, K+ ATPase.

Effects on Esophageal Acid Exposure

In patients with gastro esophageal reflux disease (GERD) and moderate to severe esophageal acid exposure, Rabeprazole 20 mg and 40 mg per day decreased 24-hour esophageal acid exposure. After seven days of treatment, the percentage of time that esophageal pH<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>4 for at least 35% of the 24-hour period; this level was achieved in 90% of subjects receiving rabeprazole 20 mg and in 100% of subjects receiving rabeprazole 40 mg. With rabeprazole 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

In patients given daily doses of rabeprazole for up to eight weeks to treat ulcerative or erosive esophagitis and in patients treated for up to 52 weeks to prevent recurrence of disease the median fasting gastrin level increased in a dose-related manner. The group median values stayed within the normal range. In a group of subjects treated daily with rabeprazole 20 mg for 4 weeks a doubling of mean serum gastrin concentrations were observed. Approximately 35% of these treated subjects developed serum gastrin concentrations above the upper limit of normal. In a study of CYP2C19 genotyped subjects in Japan, poor metabolizers developed statistically significantly higher serum gastrin concentrations than extensive metabolizers.

Endocrine Effects

Studies in humans for up to one year have not revealed clinically significant effects on the endocrine system. In healthy male volunteers treated with rabeprazole for 13 days, no clinically relevant changes have been detected in the following endocrine parameters examined: 17 ftestradiol, thyroid stimulating hormone, triiodothyronine, thyroxine, thyroxine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteotrophic hormone, prolactin, somatotrophic hormone, dehydroepiandrosterone, cortisol-binding globulin, and urinary 60-hydroxycortisol, serum testosterone and circadian cortisol profile.

Other Effects

In humans treated with rabeprazole 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 and ocular effects.

Domperidone

Domperidone is a dopamine antagonist with anti-emetic properties domperidone does not readily cross the blood-brain barrier. In domperidone users, especially in adults, extrapyramidal side effects are very rare, but domperidone promotes the release of prolactin from the pituitary. Its anti-emetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of dopamine receptors in the

chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area postrema. Animal studies, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors. Studies in man have shown oral domperidone to increase lower esophaegeal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

5.2 Pharmacokinetic Properties

Rabeprazole

After oral administration of 20 mg rabeprazole, peak plasma concentrations (Cmax) of rabeprazole occur over a range of 2.0 to 5.0 hours (Tmax). 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. The plasma half-life ranges from 1 to 2 hours.

Absorption

Absolute bioavailability for a 20 mg oral tablet of rabeprazole (compared to intravenous administration) is approximately 52%. Rabeprazole may be taken without regard to timing of meals.

Distribution

Rabeprazole is 96.3% bound to human plasma proteins. *Metabolism*

Rabeprazole is extensively metabolized. The thioether and sulphone are the primary metabolites measured in human plasma. *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.

The thioether metabolite is formed non-enzymatically by reduction of rabeprazole.

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. No unchanged rabeprazole was recovered in the urine or feces.

Domperidone

Absorption

In fasting subjects, domperidone is rapidly absorbed after oral administration, with peak plasma concentrations at 30 to 60 minutes. The low absolute bioavailability of oral domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut wall and liver. Although domperidone' s bioavailability is enhanced in normal subjects when taken after a meal, patients with gastro-intestinal complaints should take domperidone 15-30 minutes before a meal. Reduced gastric acidity impairs the

absorption of domperidone. Oral bioavailability is decreased by prior concomitant administration of cimetidine and sodium bicarbonate. The time of peak absorption is slightly delayed and the AUC somewhat increased when the oral drug is taken after a meal.

Distribution

Oral domperidone does not appear to accumulate or induce its own metabolism; a peak plasma level after 90 minutes of 21 ng/ml after two weeks oral administration of 30 mg per day was almost the same as that of 18 ng/ml after the first dose. Domperidone is 91-93% bound to plasma proteins. Distribution studies with radiolabelled drug in animals have shown wide tissue distribution, but low brain concentration. Small amounts of drug cross the placenta in rats.

Metabolism

Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. *In vitro* metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P-450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

Excretion

Urinary and fecal excretions amount to 31 and 66% of the oral dose respectively. The proportion of the drug excreted unchanged is small (10% of fecal excretion and approximately 1% of urinary excretion). The plasma half-life after a single oral dose is 7-9 hours in healthy subjects but is prolonged in patients with severe renal insufficiency.

5.3 Preclinical safety data

Non-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 List of excipients

E.H.G. Capsule Maroon/Light Yellow size "2"

6.2 Incompatibilities

None Known.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store in a cool and dry place at a temperature not exceeding 30°C. Protect from light

6.5 Nature and contents of container

10X1X10 Capsules ALU-ALU Pack

6.6 Special precautions for disposal and other handling

None Known.

7. Manufactured By

Scott-Edil Pharmacia Limited,
56, EPIP, Phase-I, Jharmajri,
Baddi, Distt. Solan- 173205 (H.P)
INDIA

8. Marketed By

Akol Healthcare Ltd.

9. Date of revision of the text

Not Applicable

10. DOSIMETRY (IF APPLICABLE)

Not applicable

11. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Not Applicable