SUMMARY PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pylotrip R

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Pylotrip contains;
Rabeprazole Sodium Tablet.....20 mg
Clarithromycin tablet.....500 mg
Two Amoxicillin capsules .....500 mg

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Moxacil 500 Capsule: A hard gelatin capsule (size # 0) having off- white color body and gray color cap imprinted 'Square" on both part containing white to. creamish white granular owder. Free from any objectionable physical defects.

Remac 500 Tablet: A light blue colored caplet shaped film coated tablet engraved 'SQUARE' on one side and a break-line on the other side.

Rabeca 20 Tablet: Yellow colored round shaped biconvex both side plain enteric coated tablet, free from any visible physical defect.

4. Clinical particulars

4.1 Therapeutic indications

Pylotrip is indicated for the eradication of *H.pylori* in active chronic gastric. duodenal and gastric ulcers.

4.2 Posology and method of administration

One Pylotrlp strip twice daily for 7-14 days or as per the physician's advice.

4.3 Contraindications

Pylotrip is contraindicated in patients with known hypersensitivity to any of its component.

4.4 Special warnings and precautions for use

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on Amoxicillin therapy. These reactions

are more appropriate to occur in individuals with a history of penicillin hypersensitivity. Clarithromycin should not be used in pregnant women except inclinical circumstances where no alternative therapy is appropriate.

4.5 Interaction with other medicinal products and other forms of interaction

Clarithromycin use in patients who are receiving theophylline may be associated with increase of serum theophylline concentrations.There have been reports of interactions of erythromycin and/or clarithromycin with carbamaz.epine, cyclosporine, tacrolimus, hexobarbital, phenytoin, alfetanil, disopyramide, lovastatin, bromocriptine, valproate, terfenadine,cisapride, pimozide & astemizole.

4.6 Pregnancy and lactation

Pylotrip R should be used during pregnancy only if the potential benefit justifies the potential
risk of the mother. Amoxicillin is excreted in human milk in very small amounts. Because of the potential for serious adverse reactions in nursing infants from Pylotrlp" R a decision should be made whether to discontinue nursing or to discontinue the drug therapy, taking into account the Importance of the therapy to the mother.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines

4.8 Undesirable effects

Adverse reactions which were reported as possibly or probably related to treatment (>3%) in clinical trials when all three components of this therapy were given concomitantly are listed below and devided by body systems. Digestive system: Nausea, vomitng, diarrhoea, dark. stools, dry mouth, glossitis, oral moniliasis, stomatitis, tongue discoloration ;Musculosk.eletal System - myalgia; Nervous System - confusion, headache,dizziness; Skin - skin reactions; Urogenital System -vaginitis, vaginal moniliasis

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Problems of overdosage with amoxicillin are unlikely to occur. Gastrointestinal symptoms (such as nausea, vomiting and diarrhoea) and disturbances of the fluid and electrolyte balances may be evident

Clarithromycin

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. One patient who had a history of bipolar disorder
ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalemia and hypoxemia. Adverse reactions accompanying overdose should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, Clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

Rabeprazole

Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg 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 dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group of Amoxicillin : penicillins with extended spectrum; ATC code: J01CA04

Pharmacotherapeutic Group of Clarithromycine: Antibacterial for systemic use, macrolide ATC Code: J01FA09
Pharmacotherapeutic group: proton pump inhibitors,
ATC code: A02B C04 Amoxicillin is a penicillin antibiotic. It acts by inhibiting the synthesis of
bacterial cell walls. It inhibits cross-linkage between the linear peptidoglycan polymer chains that make up a major component of the cell walls of both Gram-positive and Gram-negative bacteria.

Clarithromycin is a macrolide antibiotic. It prevents bacteria from growing by
interfering with their protein synthesis. It binds to the subunit SOS of the bacterial ribosome and thus inhibits the translation of peptides.

Rabeprazole sodium belongs to the class of anti-secretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H2 histamine antagonist properties, but suppress gastric acid secretion by

the specific inhibition of the H^+/K^+-ATPase enzyme (the acid or proton pump). The effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa. As a weak base, rabeprazole is rapidly absorbed following all doses and is concentrated in the acid environment of the parietal cells. Rabeprazole is converted to the active sulphenamide form through protonation and it subsequently reacts with the available cysteines on the proton pump.

5.2 Pharmacokinetic properties

Amoxicillin

Absorption

Amoxicillin fully dissociates in aqueous solution at physiological pH. Amoxicillin is stable in the acid gastric secretion and is rapidly absorbed

Cmax	T_{max}*	AUC(0-24h)	T ½
(µg/ml)	(h)	(µg.h/ml)	(h)
3.3 ± 1.12	1.5 (1.0-2.0)	26.7 ± 4.56	1.36 ± 0.56
*Median (range)			

from the gastrointestinal tract after oral administration. Following oral administration, amoxicillin is approximately 70% bioavailable. The time to peak plasma concentration (T_{max}) is approximately one hour.

The pharmacokinetic results for a study, in which an amoxicillin dose of 250 mg three times daily was administered in the fasting state to groups of healthy volunteers are presented below.

In the range 250 to 3000 the bioavailability is linear in proportion to dose (measured as C_{max} and AUC). The absorption is not influenced by simultaneous food intake. Haemodialysis can be used for elimination of amoxicillin.

Distribution

About 18% of total plasma amoxicillin is bound to protein and the apparent volume of distribution is around 0.3 to 0.41/kg. Following intravenous administration, amoxicillin has been found in gall bladder, abdominal tissue, skin, fat, muscle tissue, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

From animal studies there is no evidence for significant tissue retention of drug-derived material. Amoxicillin, like most penicillins, can be detected in breast milk (see section 4.6)

Amoxicillin has been shown to cross the placental barrier

Biotransformation

Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose.

Rabeprazole

Absorption

Rabeprazole sodium gastro-resistant tablet is an enteric-coated (gastro-resistant) tablet formulation of rabeprazole sodium. This presentation is necessary because rabeprazole is acid-labile. Absorption of rabeprazole therefore begins only after the tablet leaves the stomach. Absorption is rapid, with peak plasma levels of rabeprazole occurring approximately 3.5 hours after a 20 mg dose. Peak plasma concentrations (Cmax) of rabeprazole and AUC are linear over the dose range of 10 mg to 40 mg. Absolute bioavailability of an oral 20 mg dose (compared to intravenous administration) is about 52% due in large part to pre-systemic metabolism. Additionally the bioavailability does not appear to increase with repeat administration. In healthy subjects the plasma half-life is approximately one hour (range 0.7 to 1.5 hours), and the total body clearance is estimated to be 283 ± 98 ml/min. There was no clinically relevant interaction with food. Neither food nor the time of day of administration of the treatment affect the absorption of rabeprazole sodium.

Distribution

Rabeprazole is approximately 97% bound to human plasma proteins.

Biotransformation and Elimination

Rabeprazole sodium, as is the case with other members of the proton pump inhibitor (PPI) class of compounds, is metabolised through the cytochrome P450 (CYP450) hepatic drug-metabolising system. *In vitro* studies with human liver microsomes indicated that rabeprazole sodium is metabolised 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 cyclosporin. 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 antisecretory activity, but it is not present in plasma.

Following a single 20 mg ^{14}C-labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine.

Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites. The remainder of the dose was recovered in faeces. **Clarithromycin**

H. pylori is associated with acid peptic disease including duodenal ulcer and gastric ulcer in which about 95% and 80% of patients respectively are infected with the agent. *H. pylori* is also implicated as a major contribution factor in the development of gastric and ulcer recurrence in such patients. Clarithromycin has been used in small numbers of patients in other treatment regimens. Possible kinetic interactions have not been fully investigated. These regimens include:
Clarithromycin plus tinidazole and omeprazole; clarithromycin plus tetracycline, bismuth subsalicylate and ranitidine; clarithromycin plus ranitidine alone.
Clinical studies using various different *H. pylori* eradication regimens have shown that eradication of *H. pylori* prevents ulcer recurrence.
Clarithromycin is rapidly and well absorbed from the gastro-intestinal tract after oral administration of Clarithromycin tablets. The microbiologically active metabolite 14-hydroxyclarithromycin is formed by first pass metabolism. Clarithromycin may be given without regard to meals as food does not affect the extent of bioavailability of Clarithromycin tablets. Food does slightly delay the onset of absorption of Clarithromycin and formation of the 14-hydroxymetabolite.
The pharmacokinetics of Clarithromycin are non linear; however, steady-state is attained within 2 days of dosing. At 250 mg b.i.d. 15-20% of unchanged drug is excreted in the urine. With 500 mg b.i.d. daily dosing urinary excretion is greater (approximately 36%). The 14-hydroxyclarithromycin is the major urinary metabolite and accounts for 10-15% of the dose. Most of the remainder of the dose is eliminated in the faeces, primarily via the bile. 5-10% of the parent drug is recovered from the faeces.
When Clarithromycin 500 mg is given three times daily, the Clarithromycin plasma concentrations are increased with respect to the 500 mg twice daily dosage.
Clarithromycin provides tissue concentrations that are several times higher than the circulating drug levels. Increased levels have been found in both tonsillar and lung tissue. Clarithromycin is 80% bound to plasma proteins at therapeutic levels.
Clarithromycin also penetrates the gastric mucus. Levels of Clarithromycin in gastric mucus and gastric tissue are higher when Clarithromycin is co-administered with omeprazole than when Clarithromycin is administered alone.

5.3 Preclinical safety data

Not Applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Moxacil 500 Capsule

Purified Talc
Magnesium Stearate
Empty Hard gelatin Capsule shell (Size #0)

Rabeca 20 Tablet
Mannitol
Magnesium Oxide
Hydroxy Propyl Cellulose
Sodium Stearyl Fumarate
Absolute Ethanol
Coating
Hypromellose (5 cps)
Magnesium
oxide (heavy)
Methanol
Dichloromethane
Opadry enteric 940580000 (white)
Isopropy
l alcohol
Purified
talc
Polysorbate 80
Macrogol 6000
Ferric oxide (yellow)
Purified Water
Remac 500 mg
Tablet
Microcrystalline
Cellulose
Pregelatinized Starch
Lactose
Magnesium Stearate
Sodium Starch Glycolate (Type-A)
Colloidal Silicon Dioxide
OPADRY33G57700(Grey)
(HPMC 5cps, Titanium Dioxide, Polyethylene Glycol-3000, Lactose, Triacetin, Indigo carmene aluminium lake, FD&C Blue No. 2, Iron Oxide Yellow, Iron Oxide Black Purified water

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months (2 years)

6.4 Special precautions for storage

Do not store above 25°C & Protected from light.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Each box contains 7 Alu –Alu Blister

6.6 Special precautions for disposal <and other handling

No special requirements.

7 Marketing Authorization Holder

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