Summary of product characteristics

1. Name of the medicinal product

Rabepride Capsules

2. Qualitative and quantitative composition

Each capsule contains: Rabeprazole Sodium (enteric coated) 20mg and Itropride Hydrochloride (sustained release) capsules 150mg

Full list of excipients see Section 6.1.

3. Pharmaceutical form

Hard gelatin Capsules

4. Clinical particulars

4.1 Therapeutic indications

Rabepride Capsules is used for the treatment of Stomach acid, Gastroesophageal reflux disease, Duodenal ulcers, Functional dyspepsia, Gastrointestinal conditions.

4.2 Posology and method of administration

Oral administration

Adult: 1 capsule once daily

Swallow the medication whole. Do not chew, divide or crush the capsules

4.3 Contraindications

-Hypersensitivity to the active substances or to any of the excipients.

-Lactation and pregnancy

4.4 Special warnings and precautions for use

Itopride should be used with caution because it enhances the action of acetylcholine Rabeprazole should be used with caution in patients with severe hepatic impairment and Pregnancy.

4.5 Interaction with other medicinal products and other forms of interaction.

Rabeprazole increase elimination T1/2 of digoxin, decreases effects with amino glutethimide, carbamazepine, phenytoin and rifampin and reduces absorption of ketoconazole and itraconazole.

Anticholinergic agents reduces the action of itopride.

Food Interaction

Avoid alcohol (may irritate gastric mucosa). Rabeprazole has delayed absorption but unaltered Cmax and AUC with high-fat meals.

4.6 Fertility, pregnancy and lactation

Pregnancy

Little information is available time regarding the safe use of Rabepride capsules during pregnancy therefore it's contraindicated.

Lactation

Little information is available time regarding the safe use of Rabepride capsules during lactation therefore it's contraindicated.

Fertility

There is no information on the effects of Rabeprazole and Itropride on human fertility.

4.7 Effects on ability to drive and use machines

Do not drive or operate machinery as Rabepride capsules because alertness is impaired due to somnolence

4.8 Undesirable effects

Headache, diarrhea, dizziness, rash

Potentially Fatal: Anaphylaxis, agranulocytosis.

4.9 Overdose

There is no experience with overdose in humans. Overdose is the usual measure of gastric lavage a Symptomatic therapy.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Itopride activates gastrointestinal propulsion motility by antagonizing dopamine D2 receptors and acetyl cholinesterase inhibitory effect. Itopride activates acetylcholine release and inhibits its degradation. Itopride also has an antiemetic effect based on interaction with dopamine D2 receptors entering the chemoreceptor zone.

Itopride has a highly specific effect on the upper gastrointestinal tract. Itopride does not affect plasma gastrin concentrations.

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.

5.2 Pharmacokinetic properties

For Itopride absorption is rapidly and almost completely absorbed from the gastrointestinal tract. Relative bioavailability and 60% is given by first-pass metabolism. Food does not affect the biological availability of the product. Maximum plasma concentrations are reached 30 to 50 minutes after administration of itopride. After repeated oral dosing in the itopride and its metabolites have linear pharmacokinetics with minimal accumulation. Distribution 5/6 approximately 96% of itopride binds to Plasma proteins, predominantly albumin. The α-1-acid glycoprotein binds less than 15% of the bound itopride. Rats are extensively distributed in the tissues (Vdss = 6.1 l / kg) with the exception of the central nervous system; High concentrations are achieved in kidney, small intestine, liver, adrenal gland and stomach. Rat protein binding was lower than in humans (78% versus 96%). The transition to the CNS was minimal. Itopride passes into milk of lactating rats. Metabolism Itopride is extensively metabolised in humans in the liver. Three metabolites have been identified, only one of which shows less activity without pharmacological significance (approximately 2-3% of the effect of itopride). Itopride is metabolised by flavin monooxygenase (FMO3). The amount and potency of human FMO isoenzymes may be related to genetic polymorphism, which may lead to a rare autosomal recessive condition, known as fish odor syndrome (fish odor syndrome). The half-life of itopride may be longer in patients with trimethylaminurium. Pharmacokinetic in vivo studies of CYP-mediated reactions have not demonstrated the inhibitory or inductive effect of itopride on CYP2C19 and CYP2E1. The administration of itopride did not affect the CYP content or the

activity of dibasic glucuronyl transferase. Excreta Itopride and its metabolites are primarily excreted in the urine. The amount of urinary excreted itopride and Noxidupo administered by single oral doses to healthy volunteers was 3.7% and 75.4%, respectively. The elimination half-life of itopride was approximately 6 hours.

Absorption: Rabeprazole 20mg is an enteric-coated (gastro-resistant) formulation of rabeprazole sodium. This presentation is necessary because rabeprazole is acid-labile. Absorption of rabeprazole therefore begins only after the pellets 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 (C_{max}) 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 affects absorption of rabeprazole sodium administration of the treatment.

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 anti-secretory 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.

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 haemodialysis (creatinine clearance ≤5 ml/min/1.73 m^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 haemodialysis and 3.6 hours post dialysis. The clearance of the drug in patients with renal disease requiring maintenance haemodialysis was approximately twice that in healthy volunteers.

Hepatic dysfunction

Following a single 20 mg dose 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 pharmacodynamic 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 20 mg of rabeprazole sodium, the AUC approximately doubled, the C_{max} increased by 60 % and t½ increased by approximately 30 % as compared to young healthy volunteers. However there was no evidence of rabeprazole accumulation.

CYP2C19 Polymorphism

Following a 20 mg daily dose of rabeprazole for 7 days, CYP2C19 slow metabolisers, had AUC and t½ 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 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

Empty hard gelatin

6.2 Incompatibilities

None reported.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in a dry place, below 30°C. Protect from direct sunlight.

6.5 Nature and contents of container

Rabeprazole capsules are packed as 10 capsules in ALU-ALU blister and three such blisters contained in a unit box alongside a literature insert.

6.6 Special precautions for disposal and other handling.

No special precaution.

7. Marketing authorization holder

DAWA Limited
Plot No: 7978/9, Baba Dogo Road, Ruaraka
P.O Box 16633-00620
Nairobi- Kenya

8. Date of revision of the text: 20th May 2017.

9. Legal category: POM

1.5.2 Container labelling. ***Refer to attached Label.***