Summary of Product Characteristics for Pharmaceutical Products

1.Name of Medicinal Product

ITORPLUS

2.Qualitative and Quantitative Composition

Each hard gelatin capsule contains:
Rabeprazole sodium BP (as enteric coated pellets) .....20 mg
Itopride hydrochloride (as sustained release pellets) .....150 mg

For full list of excipients, see section 6.1.

3.Pharmaceutical Form

Hard gelatin capsules

A red color cap and transparent color body, size "2" hard gelatin capsule containing brown & white color pellets.

4.Clinical Particulars

4.1. Therapeutic indications:

Rabeprazole Sodium + Itopride Hydrochloride is primarily advocated for managing symptoms of burning in various acid peptic disorders associated with nausea and/or vomiting. It is indicated for GERD, reflux esophagitis, non-ulcer dyspepsia, gastroparesis and idiopathic hiccup, or any other acid-peptic disease accompanied by nausea and/or vomiting like acute gastritis including that induced by nonsteroidal anti-inflammatory drugs (NSAIDs).

4.2. Posology and method of administration:

MODERATE-TO-SEVERE/UNRESPONSIVE GERD/REFLUX ESOPHAGITIS: One Rabeprazole Sodium + Itopride Hydrochloride capsule once daily 15-30 minutes before food in morning for 4 to 8 weeks.

PREVENTION OF ASPIRATION PNEUMONITIS: One Rabeprazole Sodium + Itopride Hydrochloride capsule once in the evening before surgery and to be repeated on the morning of surgery.

OTHER INDICATIONS (ADULTS): One Rabeprazole Sodium + Itopride Hydrochloride capsule daily 15-30 minutes before food in morning, or as prescribed.

MAINTENANCE: One Rabeprazole Sodium + Itopride Hydrochloride capsule once daily 15-30 minutes before food in morning, or at bedtime, as prescribed.

Mode of Administration: The route of administration is oral.

4.3. Contra-indications:

Rabeprazole Sodium + Itopride Hydrochloride is not advocated to those hypersensitive to any of its ingredients, or to substituted benzimidazoles.

4.4. Special warning and precautions for use: -

Symptomatic response to rabeprazole does not preclude the presence of gastric malignancy. Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with benzimidazoles to which group rabeprazole also belongs. Rabeprazole, like other proton pump inhibitors, has potential to cause gastric carcinoids but the studies have not been conclusive. Rabeprazole Sodium + Itopride Hydrochloride capsules must not be opened, chewed or crushed; they should be swallowed as whole.

Special Precautions

Rabeprazole Sodium + Itopride Hydrochloride should be used during pregnancy only if the potential benefit justifies the probable risks involved. In view of likelihood of rabeprazole to be excreted in human milk, and because of potential for adverse reactions in nursing infants, a decision should be made whether Hydrochloride taking into account the importance of therapy to the mother. Safety and efficacy of Rabeprazole Sodium + Itopride Hydrochloride ingredients in children have not been established.

4.5 Interaction with other medicinal products and other forms of interactions:

Rabeprazole: Rabeprazole is metabolized in the liver by cytochrome P450 (CYP450). Hence, coadministration with warfarin could lead to increase in prothrombin time although it is not significant.

Even metabolism of cyclosporine is inhibited by rabeprazole when concomitantly advocated. Since Rabeprazole Sodium + Itopride Hydrochloride inhibits gastric acid secretion, it could interfere with absorption of drugs wherein gastric pH is an important determinant of bioavailability like ketoconazole.

Itopride: No interactions with regard to serum binding have been detected for itopride with warfarin, diazepam, diclofenac, ticlopidine, nifedipine and vice-versa. Metabolic interactions are not to be expected because itopride is mainly metabolized by flavin monooxygenase and not by cytochrome P450. Anticholinergic agents may reduce the action of itopride. Antiulcer agents like cimetidine, ranitidine did not affect the prokinetic action of itopride.

4.6. Use in pregnancy and lactation:

Use in Pregnancy: Rabeprazole: Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Itopride: The safety of this product in

pregnant women has not been established. Therefore, this product should only be used in pregnant women or women suspected of being pregnant, provided that the expected therapeutic benefits are evaluated to outweigh the possible risk of treatment. No teratogenic effects have been detected in animals.

Use in Lactation: Rabeprazole: Since many drugs are excreted in milk, and because of the potential for adverse reactions to nursing infants from rabeprazole, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Itopride: Itopride hydrochloride is excreted with the breast milk in lactating rats. Treatment with Itopride should be avoided during breast-feeding.

4.7. Effects on ability to drive and operate machine:

Not Applicable

4.8. Undesirable effects:

Itopride occasionally causes diarrhea/constipation, increased salivation, abdominal pain, and other gastrointestinal disturbances, hypersensitivity, headache, rarely, tremor or nausea. Galactorrhea and gynecomastia can also infrequently occur due to itopride due to increase in Prolactin levels.

The adverse effects of rabeprazole include asthenia, fever, allergic reactions, photosensitivity reactions, chills, malaise, musculoskeletal pain and aches, cardiovascular signs, digestive system complaints, thyroid abnormalities, hemopoeitic changes, edema, weight change, sleep disturbances and other central nervous symptoms, decreased libido, respiratory features, sight and hearing difficulties, d y s u r i a , genital system affections and skin lesions. There may be abnormalities in parameters tested in laboratory such as blood count, urinalysis, lipid profile, electrolytes, glucose and liver function tests on

account of rabeprazole.

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions to report any suspected adverse reactions to the National Regulatory Authority.

4.9. Overdose:

Rabeprazole: There has been no experience with large overdoses with Rabeprazole. The maximum reported overdose was 80 mg. There was no clinical signs or symptoms associated with any reported overdose. Patients with Zollinger-Ellison syndrome have been treated with up to 120 mg rabeprazole QD. No specific antidote for rabeprazole is known. Rabeprazole is extensively protein bound and is not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

Itopride: There have as yet been no reports of overdose in humans. The oral single dose LD 50 was >2000 mg/kg in mice and rats and about 600 mg/kg in dogs. In case of excessive overdosage the usual measures of gastric lavage and symptomatic therapy should be applied. Itopride does not cause QT prolongation.

5.PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Rabeprazole: Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole 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. 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%. 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 gastroesophageal reflux disease (GERD) and moderate to severe esophageal acid exposure, Rabeprazole 20 mg and 40 mg per day decreased 24-hour esophageal acid exposure.

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.

Effects on Enterochromaffin-like (ECL) Cells: Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may hyperplasia in rats and mice and gastric carcinoids in rats,

Endocrine Effects: Studies in humans for up to one year have not revealed clinically significant effects on the endocrine system.

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.

Itopride: ltopride promotes gastrointestinal motility through synergism of its dopamine D 2-receptor antagonistic action and its acetylcholine esterase inhibitory action. In addition to these actions, Itopride has an antiemetic action, which is based on its dopamine D2 receptor antagonistic action at CTZ.

5.2 Pharmacokinetic properties

Rabeprazole: Rabeprazole Sodium + Itopride Hydrochloride capsules are enteric coated to allow Rabeprazole sodium, which is acid labile to pass through the stomach relatively. 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 Cmax 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

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. *Itopride: Absorption:* On oral administration, Itopride is rapidly and extensively absorbed and peak serum concentrations are achieved within 35 minutes after oral dosing. Food does not affect its absorption.

Metabolism: Itopride is metabolized in the liver by N-oxidation to inactive metabolites by the enzyme flavin-containing monooxygenase (FMO). Biotransformation of itopride does not involve the cytochrome P450 enzyme system, thus, it is devoid of drug interaction potential with cytochrome P450 enzyme inhibitors.

Excretion: The half-life of Itopride is about 6 hours. It is excreted mainly by the kidneys as metabolites and unchanged drug. Food did not significantly affect the absorption of Itopride.

5.3 Preclinical safety data

Not Applicable,

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard gelatin capsule red/CT size "0" For Capsules

Rabeprazole sodium 20mg (EC) & Itopride 150mg (SR) Pellets

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

36 months from the date of manufacturing

6.4 Special precautions for storage

Store below 30^0C. Protect from light.

6.5 Nature and contents of container

Enteric Coated Rabeprazole Sodium and Itopride Hydrochloride Sustained Release Capsules is packed in an Alu-Alu blister of 10 Capsules, such 3 blisters are packed in a primary carton along with pack insert.

6.6 Special precautions for disposal and other handling

No special requirements.

7.Marketing Authorization Holder

WEGA HELTHCARE LTD

P.O. BOX 7326-01000

THIKA, KENYA

8.Marketing Authorization Number

H2021/CTD8600/19885

9.Date of first authorization/renewal of the authorization

September 22, 2021.

10. Date of revision of the text

September 22, 2021.