Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Name of the medicinal product: RABELEVO
Generic name: Rabeprazole Sodium and Levosulpiride Capsules

2. Qualitative and quantitative composition

Each hard gelatin capsule contains rabeprazole sodium BP 20 mg (as enteric coated pellets) and levosulpiride 75 mg (as sustained release pellets).
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Hard capsule.
Transparent red, size "2" hard gelatin capsules containing enteric coated pellets and sustained release pellets.

4. Clinical particulars

4.1 Therapeutic indications

The product is stated to be indicated for:
Helicobacter pylori infection and eradication.
Heartburn.
Gastro-oesophageal reflux disease (GORD).
Non-erosive reflux disease (NERD).
Zollinger-Ellison syndrome.
Duodenal and gastric ulcers.
Irritable bowel syndrome.

4.2 Posology and method of administration

Posology

One capsule per day on an empty stomach, or as directed by the physician.

Method of administration

For oral use, on an empty stomach.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
The drug should be used with caution in Elderly people,Children less than 14 years of age, Parkinson disease, Severe renal or hepatic insufficiency.
The drug should be used cautiously in pregnancy (only when it is expected to benefit the mother more than the possibility of risking the fetus).
The drug is known to be secreted in breast milk, so, its use should be restricted in breastfeeding women.

4.4 Special warnings and precautions for use

Rabeprazole – presence of gastric malignancy

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

Patients with healed GORD were treated for up to 40 months with rabeprazole and monitored with serial gastric biopsies. Patients without H. pylori infection (221 of 326 patients) had no clinically important pathological changes in the gastric mucosa. Patients with H. pylori infection at baseline (105 of 326 patients) had mild or moderate inflammation in the gastric body or mild inflammation in the gastric antrum. At baseline, 8% of patients had atrophy of glands in the gastric body and 15% had atrophy in the gastric antrum; at endpoint, 15% had atrophy in the gastric body and 11% in the gastric antrum. Approximately 4% of patients had intestinal metaplasia at some point during follow-up, but no consistent changes were seen.

Concomitant use with warfarin

Steady-state interactions of rabeprazole and warfarin have not been adequately evaluated in patients. There have been reports of increased INR and prothrombin time in patients receiving a proton pump inhibitor and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated concomitantly may need to be monitored.

Clostridioides difficile-associated diarrhoea

Published observational studies suggest that proton pump inhibitor therapy may be associated with an increased risk of C. difficile-associated diarrhoea, especially in hospitalised patients. This diagnosis should be considered for diarrhoea that does not improve. Patients should use the lowest dose and shortest duration of therapy appropriate to the condition being treated.

Bone fracture

Several published observational studies in adults suggest that proton pump inhibitor therapy may be associated with an increased risk of osteoporosis-related fractures of the hip, wrist or spine. The risk was increased in patients who received high-dose (multiple daily doses) and long-term therapy (a year or longer). Patients at risk of osteoporosis-related fractures should be managed according to established treatment guidelines.

Hypomagnesaemia

Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with proton pump inhibitors for at least 3 months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias and seizures. In most patients, treatment required magnesium replacement and discontinuation of the proton pump inhibitor. For patients expected to be on prolonged treatment, or who take proton pump inhibitors with medicinal products such as digoxin or medicinal products that may cause hypomagnesaemia (e.g. diuretics), monitoring of magnesium levels prior to initiation and periodically thereafter may be considered.

Concomitant use with methotrexate

Literature suggests that concomitant use of proton pump inhibitors with methotrexate, primarily at high dose, may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicity. In high-dose methotrexate administration, temporary withdrawal of the proton pump inhibitor may be considered in some patients.

Levosulpiride – populations requiring caution

The submitted document states that the product should be used with caution in elderly patients, in children under 14 years of age, in patients with Parkinson's disease, and in severe renal or hepatic insufficiency.

4.5 Interaction with other medicinal products and other forms of interaction

Rabeprazole – medicinal products metabolised by CYP450

Rabeprazole is metabolised by the CYP450 drug-metabolising enzyme system. Studies in healthy subjects have shown that rabeprazole does not have clinically significant interactions with other medicinal products metabolised by this system, such as warfarin and theophylline given as single oral doses, diazepam as a single intravenous dose, and phenytoin given as a single intravenous dose with supplemental oral dosing. Steady-state interactions have not been studied in patients.

Warfarin

There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including rabeprazole, and warfarin concomitantly. Increases may lead to abnormal bleeding and even death.

Ciclosporin

In vitro incubations with human liver microsomes indicated that rabeprazole inhibited ciclosporin metabolism with an IC50 of 62 micromolar, a concentration over 50 times higher than the Cmax in healthy volunteers following 14 days of dosing with 20 mg rabeprazole. This degree of inhibition is similar to that of omeprazole at equivalent concentrations.

Compounds dependent on gastric pH for absorption

Rabeprazole produces sustained inhibition of gastric acid secretion, so an interaction with compounds dependent on gastric pH for absorption may occur. In normal subjects, co-administration of rabeprazole 20 mg once daily resulted in an approximately 30% decrease in the bioavailability of ketoconazole and increases in the AUC and Cmax of digoxin of 19% and 29% respectively; patients may therefore need to be monitored when such medicinal products are taken concomitantly. Co-administration of rabeprazole and antacids produced no clinically relevant changes in plasma rabeprazole concentrations. Concomitant use of atazanavir and proton pump inhibitors is not recommended, as it is expected to substantially decrease atazanavir plasma concentrations and thereby reduce its therapeutic effect.

Medicinal products metabolised by CYP2C19

In a clinical study in Japan evaluating rabeprazole in adult patients categorised by CYP2C19 genotype, gastric acid suppression was higher in poor metabolisers than in extensive metabolisers, possibly due to higher rabeprazole plasma levels in poor metabolisers.

Combined administration with clarithromycin

Combined administration of rabeprazole, amoxicillin and clarithromycin resulted in increases in plasma concentrations of rabeprazole and 14-hydroxyclarithromycin. Concomitant administration of clarithromycin with other medicinal products can lead to serious adverse reactions due to drug interactions; clarithromycin is contraindicated for co-administration with certain medicinal products.

Methotrexate

Case reports, published population pharmacokinetic studies and retrospective analyses suggest that concomitant administration of proton pump inhibitors and methotrexate, primarily at high dose, may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. No formal drug interaction studies 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 sodium.

Levosulpiride

Reduced bioavailability occurs with sucralfate and with aluminium- and magnesium-containing antacids. The effect on gastrointestinal motility may be antagonised by anticholinergic agents, narcotics and analgesics. Alcohol should be avoided.

4.6 Pregnancy and Lactation

There are no adequate and well-controlled studies in pregnant women

4.7 Effects on ability to drive and use machines

Patients who experience dizziness, vertigo or somnolence while taking RABELEVO should refrain from driving or operating machinery.

4.8 Undesirable effects

Headache, dizziness, diarrhoea, constipation, stomach pain, muscle weakness, Nausea, Flatulence, Headache, Dizziness, Sleepiness, Flu-like symptoms.

Rabeprazole

Worldwide, over 2,900 patients have been treated with rabeprazole in Phase II-III clinical trials involving various dosages and durations of treatment.

Because clinical trials are conducted under varying conditions,

adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical
Studies
Experience
Adults
The data described below reflect exposure to rabeprazole sodium in 1,064 adult patients exposed for up to 8 weeks. The studies were primarily placebo- and active-controlled trials in adult patients with erosive or ulcerative GERD, duodenal ulcers and gastric ulcers. The population had a mean age of 53 years (range, 18-89 years) and had a ratio of approximately 60% male: 40% female. The racial distribution was 86% Caucasian, 8% African-American, 2% Asian, and 5% other. Most patients received 10 mg, 20 mg or 40 mg/day of rabeprazole sodium.
An analysis of adverse reactions appearing in ≥2% of rabeprazole sodium patients (n=1,064) and with a greater frequency than placebo (n=89) in controlled North American and European acute treatment trials, revealed the following adverse reactions: pain (3% vs 1%), pharyngitis (3% vs 2%), flatulence (3% vs 1%), infection (2% vs 1%), and constipation (2% vs 1%).

Three long-term maintenance studies consisted of a total of 740 adult patients; at least 54% of adult patients were exposed to rabeprazole for 6 months and at least 33% were exposed for 12 months. Of the 740 adult patients, 247 (33%) and 241 (33%) patients received 10 mg and 20 mg
of rabeprazole sodium, respectively, while 169 (23%) patients received placebo and 83 (11%) received omeprazole.

The safety profile of rabeprazole in the maintenance studies in adults was consistent with what was observed in the acute studies.

Other adverse reactions seen in controlled clinical trials, which do not meet the above criteria (≥2% of rabeprazole sodium treated patients and greater than placebo) and for which there is a possibility of a causal relationship to rabeprazole, include the following: headache, abdominal pain, diarrhoea, dry mouth, dizziness, peripheral oedema, hepatic enzyme increase, hepatitis, hepatic encephalopathy, myalgia, and arthralgia.

Combination Treatment with Amoxicillin and Clarithromycin: In clinical trials using combination therapy with RAC, no adverse reactions unique to this drug combination were observed. In the US multicentre study, the most frequently reported drug-related adverse reactions for patients who received RAC therapy for 7 or 10 days were diarrhoea (8% and 7%) and taste perversion (6% and 10%),

respectively.

No clinically significant laboratory abnormalities particular to the drug combinations were observed
For more information on adverse reactions or laboratory changes with amoxicillin or clarithromycin, refer to their respective package prescribing information, under the ADVERSE REACTIONS section.

Paediatric
In a multicentre, open-label study of adolescent patients, 12 to 16 years of age, with a clinical diagnosis of symptomatic GERD or endoscopically proven GERD, the adverse event profile was similar to that of adults. The adverse reactions reported without regard to relationship to rabeprazole sodium that occurred in ≥2% of 111 patients were headache (9.9%), diarrhoea (4.5%), nausea (4.5%), vomiting (3.6%), and abdominal pain (3.6%). The related reported adverse reactions that occurred in ≥2% of patients were headache (5.4%) and nausea (1.8%). There were no adverse reactions reported in this study that were not previously observed in adults.

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of rabeprazole sodium. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: sudden death; coma, hyper-ammonaemia; jaundice; rhabdomyolysis; disorientation and delirium; anaphylaxis; angio-oedema; bullous and other drug eruptions of the skin; severe dermatologic reactions, including toxic epidermal necrolysis (some fatal), Stevens-Johnson syndrome, and erythema multiforme; interstitial pneumonia; interstitial nephritis; TSH elevations; bone fractures; hypomagnesaemia and C. difficile-associated diarrhoea. In addition, agranulocytosis, haemolytic anaemia, leucopenia, pancytopenia and thrombocytopenia have been reported. Increases in prothrombin time/INR in patients treated with concomitant warfarin have been reported
Levosulpiride
Levosulpiride was well tolerated; the incidence of adverse events, though not negligible, were mostly mild and treatment discontinuation was infrequent. The most common adverse events were drowsiness/sedation and endocrine effects. Other side effects may include the following:

Acute muscular dystonia characterized by abnormal movements (twitching, tremor, etc.) of the hands, leg, tongue and facial muscles. Increase in plasma prolactin levels manifested by breast enlargement, production of milk, and stopping of menstrual periods. This can be taken care of with the use of lower dose of this drug. Neuroleptic malignant syndrome (characterized by muscle rigidity, suggestive of

muscle damage).
Akathisia (uncontrollable desire to move about without any anxiety).
Tardive dyskinesia, it occurs late in the therapy and its features include involuntary rhythmical movements of the face, mouth and jaw.
Weight gain.

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

4.9 Overdose
There has been no experience with large overdoses of rabeprazole. Seven reports of accidental overdose have been received; the maximum reported overdose was 80 mg and there were no clinical signs or symptoms associated with any reported overdose. Patients with Zollinger-Ellison syndrome have been treated with up to 120 mg rabeprazole daily.
No specific antidote for rabeprazole is known. Rabeprazole is extensively protein bound and is not readily dialysable. In the event of overdose, treatment should be symptomatic and supportive.

5. Pharmacological properties
5.1 Pharmacodynamic properties
Rabeprazole
Rabeprazole belongs to a class of anti-secretory compounds, the substituted benzimidazole proton pump inhibitors, which 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. 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. Rabeprazole reduces symptoms and prevents injury to the oesophagus or stomach in patients with gastro-oesophageal reflux disease or ulcers, and is also useful in conditions producing excess gastric acid such as Zollinger-Ellison syndrome.
Levosulpiride
Levosulpiride is more selective than sulpiride and acts primarily as a dopamine D2 antagonist. Its prokinetic effect is mediated through blockade of enteric (neuronal and muscular) inhibitory dopamine D2 receptors. Levosulpiride also acts as a moderate agonist at the 5-HT4 receptor; this serotonergic component may enhance its therapeutic efficacy in gastrointestinal disorders and, together with antagonism at D2 receptors, may contribute to its gastrointestinal prokinetic effect.

5.2 Pharmacokinetic properties

Rabeprazole – absorption
The capsules are enteric-coated to allow rabeprazole sodium, which is acid-labile, to pass through the stomach relatively intact. After oral administration of 20 mg rabeprazole, peak plasma concentrations occur over a range of 2.0 to 5.0 hours. Cmax and AUC are linear over an oral dose range of 10 mg to 40 mg. There is no appreciable accumulation when doses of 10–40 mg are administered every 24 hours, and the pharmacokinetics are not altered by multiple dosing. Absolute bioavailability for a 20 mg oral capsule, compared with intravenous administration, is approximately 52%. When administered with a high-fat meal the Tmax is variable and concomitant food intake may delay absorption by up to 4 hours or longer; however, Cmax and AUC are not significantly altered, so the capsules may be taken without regard to the timing of meals.
Rabeprazole – distribution
Rabeprazole is 96.3% bound to human plasma proteins.
Rabeprazole – biotransformation
Rabeprazole is extensively metabolised. A significant portion is metabolised via systemic non-enzymatic reduction to a thioether compound. Rabeprazole is also metabolised to sulphone and desmethyl compounds via cytochrome P450 in the liver. The thioether and sulphone are the primary metabolites measured in human plasma and were not observed to have significant antisecretory activity. In vitro studies have demonstrated metabolism primarily by CYP3A to a sulphone metabolite and by CYP2C19 to desmethyl rabeprazole. CYP2C19 exhibits a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3–5% of Caucasians and 17–20% of Asians); rabeprazole metabolism is slow in these sub-populations, who are referred to as poor metabolisers.
Rabeprazole – elimination
Following a single 20 mg oral dose of 14C-labelled rabeprazole, approximately 90% of the dose was eliminated in the urine, primarily as thioether carboxylic acid, its glucuronide and mercapturic acid metabolites. The remainder was recovered in the faeces. Total recovery of radioactivity was 99.8%. No unchanged rabeprazole was recovered in the urine or faeces.
Rabeprazole – special populations
Elderly: in 20 healthy elderly subjects, after oral administration of rabeprazole 20 mg once daily for 7 days, AUC values approximately doubled and Cmax increased by 60% compared with a parallel younger control group. There was no evidence of accumulation after once-daily administration.
Paediatric: in 12 adolescent patients aged 12 to 16 years with GORD receiving rabeprazole 20 mg once daily for 5 or 7 days, an approximate 40% increase in exposure was noted following 5–7 days of dosing compared with 1-day dosing. Pharmacokinetic parameters were within the range observed in healthy adult volunteers.
Gender and race: in analyses adjusted for body mass and height, rabeprazole pharmacokinetics showed no clinically significant differences between male and female subjects. In studies using different

formulations, AUC values for healthy Japanese men were approximately 50–60% greater than pooled data from healthy men in the United States.
Renal impairment: in 10 patients with stable end-stage renal disease requiring maintenance haemodialysis (creatinine clearance ≤ 5 mL/min/1.73 m^2), no clinically significant differences were observed after a single 20 mg oral dose compared with 10 healthy volunteers.
Hepatic impairment: in a single-dose study of 10 patients with chronic mild-to-moderate compensated cirrhosis administered 20 mg rabeprazole, AUC was approximately doubled, the elimination half-life was 2- to 3-fold higher and total body clearance was decreased to less than half compared with healthy men. In a multiple-dose study of 12 patients with mild-to-moderate hepatic impairment administered 20 mg once daily for 8 days, AUC and Cmax increased by approximately 20% compared with healthy matched subjects; these increases were not statistically significant. No information exists on rabeprazole disposition in patients with severe hepatic impairment.
Combined administration with antimicrobials: in 16 healthy volunteers genotyped as extensive metabolisers with respect to CYP2C19, the AUC and Cmax for clarithromycin and amoxicillin were not different following combined administration compared with single administration; however, rabeprazole AUC and Cmax increased by 11% and 34% respectively, and the AUC and Cmax for 14-hydroxyclarithromycin increased by 42% and 46% respectively. This increase is not expected to produce safety concerns.
Concomitant use with clopidogrel: in a study of healthy subjects receiving clopidogrel 75 mg once daily with placebo or with rabeprazole sodium 20 mg for 7 days, the mean AUC of the active metabolite of clopidogrel was reduced by approximately 12% (mean AUC ratio 88%, 90% CI 81.7–95.5%).

Levosulpiride

Oral bioavailability is about 30% and peak plasma concentrations occur after about 3 hours. Excretion is mainly via the urine. The plasma half-life is 9.7 hours after oral administration and 4.3 hours after intravenous administration.

5.3 Preclinical safety data

Not applicable

6. Pharmaceutical Particulars

6.1 List of Excipients

RABEPRAZOLE Enteric coated pellets and Levosulpiride sustained release blended pellets
Capsules “2” Trans Red

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

36 months.

6.4 Special Precautions for storage

Store in a cool, dry place. Protect from light.

6.5 Nature and Content of container

Alu-Alu blister containing 10 capsules; one such blister is packed in a carton together with the package insert.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorization Holder

Nedah Pharma Ltd.
P.O. Box 6625-00300, Nairobi, Kenya.

Manufacturer

Curis Lifesciences Pvt. Limited
PF-23, Sanand GIDC II, Sanand – 382110, India.

8. Marketing Authorization Number

H2022/CTD9174/18753

9. Date of first authorization/renewal of the authorization

2023 May 03

10. Date of revision of the text

2023 May 03