1. NAME OF THE MEDICINAL PRODUCT

Dexpure (Dexrabeprazole Sodium Tablets 10mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each enteric coated tablet contains:
Dexrabeprazole sodium……10 mg
Excipients…..q.s.
Colour: Titanium Dioxide BP

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

White coloured round shaped enteric coated tablet.

4. Clinical particulars

4.1 Therapeutic indications

Gastro- oesophageal reflux disease.
Active benign and active duodenal ulcer.

4.2 Posology and method of administration

Posology
Adults
The usual dosage in adults is 10mg once daily in the morning for 4-8 weeks depending upon response of patient.
Maintenance of healing of GERD may suffice with a lower dose of 5 mg once daily. Use in special population
Renal impairment
Caution may be necessary for patients with renal impairment, basis the clinical condition.
Hepatic impairment
Caution may be necessary for patients with hepatic impairment, basis the clinical condition
Elderly
Basis the decreased hepatic, renal and cardiac function in elderly patients, caution may be required before giving Dexpure.
Children
The safety and effectiveness of dexrabeprazole in pediatric patients has not been established.
Method of administration
Dexrabeprazole Sodium tablets should not be chewed or crushed, but should be swallowed whole.

4.3 Contraindications

- Dexpure is contraindicated in patients with known hypersensitivity to dexrabeprazole sodium, substituted benzimidazole or to any component of the formulation.
- Dexrabeprazole is contraindicated in pregnancy and during breast-feeding.

4.4 Special warnings and precautions for use

The special warnings and precautions with rabeprazole shall also be applicable for dexrabeprazole and the same has been discussed below:

Symptomatic response to therapy with rabeprazole does not preclude the presence of gastric or oesophageal malignancy, therefore the possibility of malignancy should be excluded prior to commencing treatment with rabeprazole sodium.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

A risk of cross-hypersensitivity reactions with other proton pump inhibitor (PPI) or substituted benzimidazoles cannot be excluded.

There have been post marketing reports of blood dyscrasias (thrombocytopenia and neutropenia). In the majority of cases where an alternative aetiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole.

Hepatic enzyme abnormalities have been seen in clinical trials and have also been reported. In the majority of cases where an alternative aetiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole.

No evidence of significant drug related safety problems was seen in a study of patients with mild to moderate hepatic impairment versus normal age and sex matched controls. However because there are no clinical data on the use of rabeprazole in the treatment of patients with severe hepatic dysfunction, the prescriber is advised to exercise caution when treatment with rabeprazole is first initiated in such patients.

<u>Co-administration of atazanavir with rabeprazole is not recommended.</u>

Treatment with PPIs, including rabeprazole sodium, may possibly increase the risk of gastrointestinal infections such as Salmonella, Campylobacter and Clostridium difficle.

PPIs, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in older people or in presence of other recognised risk factors. Observational studies suggest that PPIs may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Severe hypomagnesemia, has been reported in patients treated with PPIs like rabeprazole sodium for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels prior to initiation of PPI treatment and periodically during treatment.

<u>Concomitant use of rabeprazole with methotrexate</u>:

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients.

Influence on vitamin B12 absorption:
All acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or a- chlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy or if respective clinical symptoms are observed.

Subacute cutaneous lupus erythematosus (SCLE):
PPIs are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping rabeprazole sodium. SCLE after previous treatment with a PPI may increase the risk of SCLE with other PPIs.

Interference with laboratory tests:
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, rabeprazole sodium treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of PPI treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Dexrabeprazole does not have clinically significant interactions with drugs metabolized through CYP450 like warfarin, theophylline, diazepam and phenytoin.

The drug interactions with rabeprazole shall also be applicable for dexrabeprazole and the same has been discussed below:

Rabeprazole sodium produces a profound and long lasting inhibition of gastric acid secretion. An interaction with compounds whose absorption is pH dependent may occur. Co-administration of rabeprazole sodium with ketoconazole or itraconazole may result in a significant decrease in antifungal plasma levels. Therefore, individual patients may need to be monitored to determine if a dosage adjustment is necessary when ketoconazole or itraconazole are taken concomitantly with rabeprazole.
In clinical trials, antacids were used concomitantly with the administration of rabeprazole and, in a specific drug-drug interaction study, no interaction with liquid antacids was observed.
Co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg once daily) to healthy volunteers resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Although not studied, similar results are expected with other PPIs. Therefore, PPIs including rabeprazole, should not be co- administered with atazanavir.
Studies in healthy subjects have shown that rabeprazole sodium does not have clinically

significant interactions with amoxicillin. Rabeprazole does not adversely influence plasma concentrations of amoxicillin or clarithromycin when co-administered for the purpose of eradicating upper gastrointestinal *H. pylori* infection.
No interaction is expected between rabeprazole and cyclosporin.

Methotrexate
Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted.

4.6 Pregnancy and Lactation

Pregnancy
There are no adequate and well-controlled studies in pregnant women.
Dexrabeprazole is contraindicated during pregnancy.
Lactation
There are no studies in lactating women and it is not known whether dexrabeprazole sodium is excreted in breast milk. Therefore, dexrabeprazole should not be used during breast-feeding.

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.

4.8 Undesirable effects

Dexrabeprazole was well tolerated during clinical trials. Adverse effects reported during post-marketing study were: headache, diarrhea, nausea, malaise, skin eruptions, dizziness, itching, dryness of mouth, dryness of skin, drowsiness, fatigue, constipation, abdominal fullness, arthralgias, vomiting, loss of appetite, breathlessness.
The adverse events with rabeprazole shall also be applicable for dexrabeprazole and the same has been discussed below:
The most commonly reported adverse drug reactions, during controlled clinical trials with rabeprazole were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth. The majority of adverse events experienced during clinical studies were mild or moderate in severity, and transient in nature.
The following adverse events have been reported from clinical trial and post-marketing experience.

Frequencies are defined as: Common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

System organ class	**Frequency**	**Adverse reactions**
Infections and infestations	**Common**	Infection

Blood and lymphatic system disorders	**Rare**	Neutropenia Leucopenia Thrombocytopenia Leucocytosis
Immune system disorders	**Rare**	Hypersensitivity[1,2]
Metabolism and nutrition disorders	**Rare**	Anorexia
	Not Known	Hyponatremia Hypomagnesaemia[4]
Psychiatric disorders	**Common**	Insomnia
	Uncommon	Nervousness
	Rare	Depression
	Not Known	Confusion
Nervous system disorders	**Common**	Headache Dizziness
	Uncommon	Somnolence
Eye disorders	**Rare**	Visual disturbance
Vascular disorders	**Not Known**	Peripheral Oedema
Respiratory, thoracic and mediastinal disorders	**Common**	Cough Pharyngitis Rhinitis
	Uncommon	Bronchitis Sinusitis
Gastrointestinal disorders	**Common**	Diarrhoea Vomiting Nausea
		Abdominal pain Constipation Flatulence Fundic Gland Polyps (Benign)
	Uncommon	Dyspepsia Dry mouth Eructation
	Rare	Gastritis Stomatitis Taste disturbance
	Not Known	Microscopic colitis

Hepato-biliary disorders	**Rare**	Hepatitis Jaundice Hepatic encephalopathy3
Skin and subcutaneous tissue disorders	**Uncommon**	Rash Erythema2
	Rare	Pruritus Sweating Bullous reactions2
	Very Rare	Erythema multiforme, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS)
	Not Known	Subacute cutaneous lupus erythematosus4
Musculoskeletal connective tissue and bone disorders	**Common**	Non-specific pain Back pain
	Uncommon	Myalgia Leg cramps Arthralgia Fracture of the hip, wrist or spine4
Renal and urinary disorders	**Uncommon**	Urinary tract infection
	Rare	Interstitial nephritis
Reproductive system and breast disorders	**Not Known**	Gynecomastia
General disorders and administration site conditions	**Common**	Asthenia Influenza like illness
	Uncommon	Chest pain Chills Pyrexia
Investigations	**Uncommon**	Increased hepatic enzymes3
	Rare	Weight increased

1: Includes facial swelling, hypotension and dyspnoea

2: Erythema, bullous reactions and hypersensitivity reactions have usually resolved after discontinuation of therapy.
3: Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis. In treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with rabeprazole is first initiated in such patients.
4: See Special warnings and precautions for use.

4.9 Overdose

There has been no experience with large overdoses with dexrabeprazole sodium tablets. 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 Pharmacodynamics properties:

Pharmacotherapeutic group: Alimentary tract and metabolism, Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), PPIs, ATC code: A02BC07

Mechanism of action

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. 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

Clinical study

In a multicentric, randomized, double-blind, comparative clinical trial conducted by Emcure, the efficacy and safety of Dexrabeprazole 10 mg, taken orally for 28 days, for the treatment of Gastro Esophageal Reflux Disease (GERD) was evaluated in a total of one hundred and sixty patients. The primary efficacy variables were

- patients were asked to mark the severity of their GERD symptoms (heart burn, regurgitation, bloating, nausea and dysphagia) on a Visual Analogue Scale (VAS) of 0 mm to 100 mm at each visit.
- record presence or absence of GERD symptoms daily in the diary throughout the study duration.
- assessment of adverse drug reactions at each visit.

It was found that, after 14 days of therapy both Dexrabeprazole 10 mg and the racemate Rabeprazole 20 mg film-coated tablets showed statistically significant ($p<0.01$) improvement in the VAS mean scores for all the symptoms. This improvement was maintained even at 28 days. Day 28 values were superior and statistically significant ($p<0.01$) to the day 14 values with respect to all the parameters in both the groups.

The comparative difference between the reference and test product on either day 14 or day 28 was not statistically significant as per this study ($p>0.05$) except possibility for dysphagia in favour of reference although the lower limit of 95% confidence interval for the difference was very close to zero and therefore may be ignored. The subgroup analysis of efficacy in NSAID induced gastritis and GERD patients were similar to the findings of the overall study group. This confirmed the efficacy of the test product even in this difficult to treat sub-group. The results of the endoscopy showed that the incidence of the residual esophagitis after 28 days therapy was higher in the reference group (65%) compared to the test group (38%), which represented an absolute reduction of 27% and relative risk reduction of 42%. The investigator reported improvement in endoscopic findings showed satisfaction of 95.2% in the Dexrabeprazole group compared to the 65.2% reduction in the racemate Rabeprazole group ($P=0.036$, Chi-square). Hence endoscopy results favour the test product over the reference product. There was no patient in any group which reported any adverse reaction. With regard to improvement in the endoscopic findings and healing of lesions, Dexrabeprazole was better than the racemate even if used at half of the dose. Dexrabeprazole was safe and effective in the management of the gastro-esophageal reflux disease. The efficacy of Dexrabeprazole was comparable to the Rabeprazole 20 mg. There were no changes in renal, hepatic, and hematologic indices of safety. Both the groups were equally effective even in the NSAID induced gastritis and GERD sub-group. Hence it would be appropriate to recommend Dexrabeprazole at half the dose of the racemate for the management of GERD.

5.2 Pharmacokinetic properties

After oral administration of 20mg tablet, peak plasma concentration (C_{max}) 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 10mg to 40mg. There is no appreciable accumulation when doses of 10mg to 40mg are administered every 24 hours, the pharmacokinetics of rabeprazole are not altered by multiple dosing. The plasma half-life ranges from 1 to 2 hours.

Following oral administration of 20mg, rabeprazole is absorbed and can be detected in plasma by 1 hour. Absolute bioavailability for a 20mg oral tablet of rabeprazole (compared to intravenous administration) is approximately 52%. Rabeprazole is 96.3% bound to human plasma proteins. Following a single 20mg oral dose of 14C labelled rabeprazole, approximately 90% of the drug was eliminated in the urine, primarily carboxylic acid, its glucuronide, and mercapturic acid metabolites.

5.3 Preclinical safety data

The acute lethal oral dose of R (+)- Rabepraprazole sodium, in Sprague Dawley rats was found to be greater than 200mg mg/kg body weight.

The no observed adverse effect level (NOAEL) of dexrabeprazole sodium, in the Sprague dawley rat via oral route, over a period of 90 days was found to be 7.5mg/kg body weight in male and female animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Hydroxy Propyl Cellulose
Light Magnesium Oxide
Mannitol
Hydroxy Propyl cellulose
Isopropyl Alcohol
Mannitol DC Grade
Magnesium Stearate
Titanium Dioxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store in a cool & dry place, below 30°C.

6.5 Nature and contents of container
10 Tablets are packed in Alu-Alu blister and such 3 blisters are packed in carton along with pack insert.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION
Emcure Nigeria Limited

8. DRUG PRODUCT MANUFACTURER
Emcure Pharmaceuticals Limited
Lane No. 3, Phase-ll, SIDCO Industrial Complex
Bari-Brahmana, Jammu (J&K)- 181133, INDIA

9. NAFDAC REGISTRATION NUMBER(S)
A4-8176

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13.12.2024