1.17 SUMMARY PRODUCT CHARACTERISTICS (SPC)

1.17.1 PRODUCT INFORMATION FOR HEALTH PROFESSIONALS (FOR ALL PRODUCTS SUBJECT TO MEDICAL PRESCRIPTION)

1. NAME OF THE MEDICINAL PRODUCT

Naproxene Delayed-Release and Esomeprazole Tablets (XENOZ)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated bilayered tablet contains:

Esomeprazole Magnesium Trihydrate BP	
Eq. to Esomeprazole	20 mg
Naproxene Sodium BP	500 mg
(As Delayed-release form)	
Excipients	Q.S.
Colour: Red Oxide of Iron	

3. PHARMACEUTICAL FORM

Solid oral dosage form, tablets

An off white/light orange color, elongated shape biconvex bilayered with brick red colour, film coated tablet having a break line on one side of each tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It is a fixed combination of naproxen, a non-steroidal anti-inflammatory drug, and esomeprazole, a proton pump inhibitor (PPI) indicated for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID associated gastric ulcers.

Limitations of Use: It is not interchangeable with the individual components of naproxen and esomeprazole magnesium.

4.2 Posology and method of administration

One tablet twice daily. Should be avoided in moderate/severe renal insufficiency or in severe hepatic insufficiency. Consider dose reduction in mild/moderate hepatic insufficiency.

Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.

The tablets are to be swallowed whole with liquid. Do not split, chew, crush or dissolve the tablet. It is to be taken at least 30 minutes before meals.

5. SAFETY INFORMATION

5.1 Contraindications

Known hypersensitivity to naproxen, esomeprazole magnesium, substituted benzimidazoles, or to any components of the drug product including omeprazole. History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. In the setting of coronary artery bypass graft (CABG) surgery.

5.2 Special Warnings and Special Precautions for Use

- Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop.
- Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure.
- Heart Failure and Edema: Avoid use of tablet in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure.
- Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of tablet in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function.
- Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs.
- Exacerbation of Asthma Related to Aspirin Sensitivity: It is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma.

- Serious Skin Reactions: Discontinue tablet at first appearance of skin rash or other signs of hypersensitivity.
- Premature Closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks gestation.
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs of symptoms of anemia.
- Masking of Inflammation and Fever: Potential for diminished utility of diagnostic signs in detecting infections.
- Laboratory Monitoring: Obtain CBC and chemistry profile periodically during treatment. Monitor hemoglobin periodically in patients on long term treatment who have an initial value of 10 g or less.
- Active Bleeding: Withdraw treatment in patients who experience active and clinically significant bleeding.
- Concomitant NSAID Use: Do not use it with other naproxen containing products or other non-aspirin NSAIDs.
- Gastric Malignancy: In adults, symptomatic response to esomeprazole does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing.
- Acute Interstitial Nephritis: Observed in patients taking PPIs.
- Clostridium difficile-Associated Diarrhea: PPI therapy may be associated with increased risk of Clostridium difficile associated diarrhea.
- Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine.
- Cutaneous and Systemic Lupus Erythematosus: Mostly cutaneous, new onset or exacerbation of existing disease; discontinue it and refer to specialist for evaluation.
- Interaction with Clopidogrel: Avoid concomitant use.
- Cyanocobalamin (Vitamin B-12) Deficiency: Daily long-term use (e.g., longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin.
- Hypomagnesemia: Reported rarely with prolonged treatment with PPIs.
- Interaction with St. John’s Wort or Rifampin: Avoid concomitant use.

- Interactions with Diagnostic Investigations for Neuroendocrine Tumors: Increases in intragastric pH may result in hypergastrinemia, enterochromaffin-like cell hyperplasia, and increased Chromogranin A levels which may interfere with diagnostic investigations for neuroendocrine tumors.
- Interaction with Methotrexate: Concomitant use with PPIs may elevate and/or prolong serum concentrations of methotrexate and/or its metabolite, possibly leading to toxicity.

5.3 Pregnancy and Lactation

Pregnancy

Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation.

Females and Males of Reproductive Potential: NSAIDs are associated with reversible infertility. Consider withdrawal of tablets in women who have difficulties conceiving.

5.4 Undesirable Effects

The following adverse experiences have been reported in patients taking tablets during clinical trials:

	Very Common	**Common**	**Uncommon**	**Rare**
Infections and infestations			infection	diverticulitis
Blood and lymphatic system disorders				eosinophilia, leucopenia
Immune system disorders				hypersensitivity reactions
Metabolism and nutrition disorders			appetite disorder	fluid retention, hyperkalemia, hyperuricemia
Psychiatric disorders			anxiety, depression, insomnia	confusion, dream abnormalities
Nervous system		dizziness,	paraesthesia,	somnolence,

disorders		headache, taste disturbance	syncope	tremor
Ear and labyrinth disorders			tinnitus, vertigo	
Cardiac disorders			arrhythmia, palpitations	myocardial infarction, tachycardia
Vascular disorders		hypertension		
Respiratory, thoracic and mediastinal disorders			asthma, bronchospasm, dyspnea	
Gastrointestinal disorders	dyspepsia	abdominal pain, constipation, diarrhoea, esophagitis, flatulence, gastric/duodenal ulcers*, gastritis, nausea, vomiting	dry mouth, eructation, gastrointestinal bleeding, stomatitis	glossitis, hematemesis, rectal bleeding
Skin and subcutaneous tissue disorders		skin rashes	dermatitis, hyperhidrosis, pruritus, urticaria	alopecia, ecchymoses
Musculoskeletal and connective tissue disorders		arthralgia	myalgia	
Renal and urinary disorders				proteinuria, renal failure
Reproductive system and breast disorders				menstrual disorder
General disorders and administration site disorders		oedema	asthenia, fatigue, pyrexia	
Investigations			abnormal liver function tests, raised serum creatinine	

5.5 Overdosage

Overdosage of naproxen:

Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred but were rare

Overdosage of esomeprazole: A single oral dose of esomeprazole at 510 mg/kg (about 124 times the human dose on a body surface area basis) was lethal to rats. The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia, and intermittent clonic convulsions. The symptoms described in connection with deliberate esomeprazole overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg of esomeprazole were uneventful. Reports of overdosage with omeprazole in humans may also be relevant. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience. No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of overdosage, treatment should be symptomatic and supportive.

6. PHARMACOLOGICAL PROPERTIES

6.1 PHARMACODYNAMIC PROPERTIES

Naproxen is a potent inhibitor of prostaglandin synthesis in vitro. Naproxen concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because naproxen is an inhibitor of prostaglandin synthesis, its mode of action may be due to an increase of prostaglandins in peripheral tissues.

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. Esomeprazole is protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related up to a daily dose of 20 to 40 mg and leads to inhibition of gastric acid secretion.

6.2 PHARMACOKINETIC PROPERTIES

Absorption of Naproxen

At steady state following administration of tablet twice daily, peak plasma concentrations of naproxen are reached on average 3 hours following both the morning and the evening dose. Bioequivalence between esomeprazole and enteric-coated naproxen, based on both area under the plasma concentration-time curve (AUC) and maximum plasma concentration (Cmax) of naproxen, has been demonstrated for 500 mg doses.

Naproxen is absorbed from the gastrointestinal tract with an *in vivo* bioavailability of 95%. Steady-state levels of naproxen are reached in 4 to 5 days.

Absorption of Esomeprazole

Following administration of tablet twice daily, esomeprazole is rapidly absorbed with peak plasma concentration reached within on average, 0.43 to 1.2 hours, following the morning and evening dose on both the first day of administration and at steady state. The peak plasma concentrations of esomeprazole are higher at steady state compared to on first day of dosing of tablet.

Distribution of Naproxen

Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels naproxen is greater than 99% albumin-bound. At doses of naproxen greater than 500 mg/day there is less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses (average trough Css 36.5, 49.2 and 56.4 mg/L with 500, 1000 and 1500 mg daily doses of naproxen, respectively). The naproxen anion has been found in the milk of lactating

women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma.

Distribution of Esomeprazole

The apparent volume of distribution at steady state in healthy subjects is approximately 16L. Esomeprazole is 97% plasma protein bound.

Metabolism of Naproxen

Naproxen is extensively metabolized in the liver by the cytochrome P450 system (CYP), CYP2C9 and CYP1A2, to 6-0-desmethyl naproxen. Neither the parent drug nor the metabolites induce metabolizing enzymes. Both naproxen and 6-0-desmethyl naproxen are further metabolized to their respective acylglucuronide conjugated metabolites. Consistent with the half-life of naproxen, the area under the plasma concentration time curve increases with repeated dosing of tablet twice daily.

Metabolism of Esomeprazole

Esomeprazole is extensively metabolized in the liver by the CYP enzyme system. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxyl-and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma. The major metabolites of esomeprazole have no effect on gastric acid secretion.

The area under the plasma esomeprazole concentration-time curve increases with repeated administration of tablet. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. An increased absorption of esomeprazole with repeated administration of tablet probably also contributes to the time-and dose-dependency.

Excretion of Naproxen

Following administration of tablet twice daily, the mean elimination half-life for naproxen is approximately 15 hours following the evening dose, with no change with repeated dosing.

The clearance of naproxen is 0.13 mL/min/kg. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (<1%), 6-0-desmethyl naproxen (<1%) or their conjugates (66% to 92%). Small amounts, 3% or less of the

administered dose, are excreted in the feces. In patients with renal failure, metabolites may accumulate.

Excretion of Esomeprazole

Following administration of tablet twice daily, the mean elimination half-life of esomeprazole is approximately 1 hour following both the morning and evening dose on day 1, with a slightly longer elimination half-life at steady state (1.2-1.5 hours). Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the feces. Less than 1% of the parent drug is found in the urine.

6.3 Preclinical safety data

None

7. PHARMACEUTICAL PARTICULARS

7.1 List of excipients

Microcrystalline Cellulose	BP
Calcium sulfate dihydrate	BP
Maize starch	BP
Povidone K 30	BP
Isopropyl Alcohol	BP
Purified talc	BP
Magnesium stearate	BP
Crospovidone	BP
Croscarmellose Sodium	BP
Colloidal anhydrous silica	BP
Calcium carbonate	BP
HPMC* Phthalate	BP
Sodium starch glycollate	BP
Colour: Red oxide of Iron	IHS
Instacoat moist shield	IHS
Dichloromethane	BP

7.2 Incompatibilities

None

7.3 Shelf life

2 years

7.4 Special precautions for storage

Store below 30°C. Protect from light and moisture

7.5 Nature and contents of container

An off white/light orange color, elongated shape biconvex bilayered with brick red colour, film coated tablet having a break line on one side of each tablet.

7.6 Special precautions for disposal and other handling

No Special Requirements.

8. MARKETING AUTHORISATION HOLDER

SALUD CARE (I) PRIVATE LIMITED
435, Kishanpur Jamalpur,
Opp. Pharma College of Roorkee,
Roorkee- 247 661
Haridwar, Uttarakhand,
INDIA

9. MARKETING AUTHORISATION NUMBER(S)

Not applicable.

10. DATE OF REVISION OF TEXT

Not applicable.