Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

XENOZ 500mg/20mg film-coated bi-layered tablet

2. Qualitative and quantitative composition

Each film-coated bilayered tablet contains:

22.17 mg Esomeprazole Magnesium Trihydrate BP Eq. to Esomeprazole 20 mg

505 mg Naproxene Sodium BP 500 mg (As Delayed-release form)

Excipients of known effect: Each film-coated bilayered tablet contains 28.83 mg Microcrystalline Cellulose BP.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated bilayered 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,
- Ankylosing spondylitis
- Acute musculoskeletal disorders (such as sprains and strains, direct trauma, lumbosacral pain, cervical spondylitis, tenosynovitis, and fibrositis)

Esomeprazole functions 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

Posology

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms, but this should be consistent with individual patient treatment goals.

One tablet twice daily.

Should be avoided in moderate/severe renal insufficiency or severe hepatic insufficiency

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.

Adults

Xenoz tablets should be swallowed whole and not broken or crushed.

Therapy should be started at the lowest recommended dose, especially in older people.

- *Rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis*

The usual dose is a 500/20mg tablet twice daily taken at 12-hour intervals. In the following cases, a loading dose of 1000mg/40mg per day for the acute phase is recommended:

a) In patients reporting severe night-time pain/or morning stiffness.

b) In patients being switched to Naproxen from a high dose of another anti-rheumatic compound.

c) In osteoarthrosis, where pain is the predominant symptom.

- *Acute musculoskeletal disorders and dysmenorrhoea*

1 tablet twice daily

Older people

Studies indicate that although the total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in older people. The implication of this finding for Xenoz dosing is unknown. As with other drugs used in older people, it is prudent to use the lowest effective dose and for the shortest possible duration, as older people are more prone to adverse events.

Paediatric population

Xenoz is not recommended for children below the age of 16. Naproxen is implicated in this case.

Renal/ hepatic impairment

A lower dose should be considered in patients with renal or hepatic impairment. Xenoz is contraindicated in patients with baseline creatinine clearance less than 30 ml/minute because accumulation of naproxen metabolites has been seen in patients with severe renal failure or those on dialysis.

Treatment should be reviewed at regular intervals and discontinued if no benefit is seen.

Method of administration

For oral administration.

4.3 Contraindications

Known hypersensitivity to naproxen, esomeprazole magnesium, substituted benzimidazoles, any excipients, or to any components of the drug product, including omeprazole.

Since the potential exists for cross-sensitivity reactions, Xenoz should not be given to patients in whom aspirin or other non-steroidal anti-inflammatory/analgesic drugs induce asthma, rhinitis, nasal polyps or urticaria. These reactions have the potential of being fatal. Severe anaphylactic-like reactions to naproxen have been reported in such patients.

Severe renal, hepatic or heart failure

Xenoz is not recommended in pregnancy. Naproxen is contraindicated during the last trimester of pregnancy

4.4 Special warnings and 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 the tablet in patients with severe heart failure unless benefits are expected to outweigh the 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 of 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 an 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 a 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.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of antacid or colestyramine can delay the absorption of naproxen but does not affect its extent. Concomitant administration of food can delay the absorption of naproxen, but does not affect its extent.

Due to the high plasma protein binding of naproxen and esomeprazole, patients simultaneously receiving hydantoins, anticoagulants, other NSAIDs, aspirin or a highly protein-bound sulfonamide should be observed for signs of overdosage of these drugs. Patients simultaneously receiving Naproxen and a hydantoin, sulfonamide or sulfonylurea should be observed for adjustment of dose if required.

It is considered unsafe to take NSAIDs in combination with anti-coagulants such as warfarin or heparin unless under direct medical supervision, as NSAIDs may enhance the effects of anti-coagulants.

Acetylsalicylic acid

Clinical pharmacodynamic data suggest that concomitant naproxen usage for more than one day consecutively may inhibit the effect of low-dose acetylsalicylic acid on platelet activity and this inhibition may persist for up to several days after stopping naproxen therapy. The clinical relevance of this interaction is not known.

Other analgesics including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects.

No interactions have been observed in clinical studies with naproxen and anticoagulants or sulphonylureas, but caution is nevertheless advised since interaction has been seen with other non-steroidal agents of this class.

Caution is advised when Xenoz is co-administered with diuretics as there can be a decreased diuretic effect. The natriuretic effect of furosemide has been reported to be inhibited by some drugs of this class. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Inhibition of renal lithium clearance leading to increases in plasma

lithium concentrations has also been reported.

Naproxen in Xenoz and other non-steroidal anti-inflammatory drugs can reduce the anti- hypertensive effect of anti-hypertensives. Concomitant use of NSAIDs with ACE inhibitors or angiotensin-II receptor antagonists may increase the risk of renal impairment, especially in patients with pre-existing poor renal function.

Probenecid given concurrently increases naproxen plasma levels and extends its half- life considerably.

Caution is advised where methotrexate is administered concurrently because of possible enhancement of its toxicity, since naproxen, in common with other non- steroidal anti-inflammatory drugs, has been reported to reduce the tubular secretion of methotrexate in an animal model.

NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels when co-administered with cardiac glycosides.
As with all NSAIDs caution is advised when ciclosporin is co-administered because of the increased risk of nephrotoxicity.

NSAIDs should not be used for 8 - 12 days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.

As with all NSAIDs, caution should be taken when co-administering with corticosteroids because of the increased risk of gastrointestinal ulceration or bleeding.

Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking quinolones may have an increased risk of developing convulsions.

There is a possible risk of nephrotoxicity when NSAIDs are given with tacrolimus.

There is an increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.
It is suggested that Naproxen therapy be temporarily discontinued 48 hours before adrenal function tests are performed, because Naproxen may artifactually interfere with some tests for 17-ketogenic steroids. Similarly, naproxen may interfere with some assays of urinary 5-hydroxyindoleacetic acid.

4.6 Pregnancy and Lactation

Pregnancy

From the 20th week of pregnancy onward, Naproxen use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid the use of NSAIDs in pregnant women starting at 30 weeks gestation as they cause:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);
the mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

Breast feeding

Naproxen has been found in the milk of lactating women. The use of Xenoz should therefore be avoided in patients who are breastfeeding.

Females and Males of Reproductive Potential

NSAIDs are associated with reversible infertility. Consider the withdrawal of tablets in women who have difficulties conceiving.

Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern.

4.7 Effects on the ability to drive and use machines

Some patients may experience drowsiness, dizziness, vertigo, insomnia, fatigue, visual disturbances or depression with the use of Xenoz. If

patients experience these or similar undesirable effects, they should not drive or operate machinery.

4.8 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 disorders		dizziness, headache, taste disturbance	paraesthesia, syncope	somnolence, 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	

4.9 Overdose

Overdosage of naproxen

Symptoms following acute NSAID overdosages have typically been 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 over 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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Naproxen

Pharmacotherapeutic group: Antiinflamatory & antirheumatic products
ATC Code: M01AE52

Esomeprazole
Pharmacotherapeutic group: Drugs for acid related disorders, proton pump inhibitors
ATC code: A02BC05

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 in 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.

5.2 Pharmacokinetic properties

<u>Absorption of Naproxen</u>

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 16 L. 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 the 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 the tablet. This increase is dose-dependent and results in a nonlinear dose-AUC relationship after repeated administration. An increased absorption of esomeprazole with repeated administration of the tablet probably also contributes to the time- and dose-dependency.

Excretion of Naproxen

Following administration of a 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 from any dose is excreted in the urine, primarily as 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 the 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.

5.3 Preclinical safety data

Naproxen

Fertility

Naproxen did not affect the fertility of rats when administered orally at doses of 30mg/kg/day to males and 20mg/kg/day to females.

Teratogenicity

Naproxen was not teratogenic when administered orally at doses of 20mg/kg/day during organogenesis to rats and rabbits.

Perinatal/Postnatal Reproduction

Oral administration of naproxen to pregnant rats at doses of 2, 10, and 20mg/kg/day during the third trimester of pregnancy resulted in difficult labour. These are known effects of this class of compounds and were demonstrated in pregnant rats with aspirin and indomethacin.

Esomeprazole

Non-clinical data reveal no particular hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and toxicity to reproduction and development. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows: Carcinogenicity studies in the rat with the racemic mixture have shown gastric ECL-cell hyperplasia and carcinoids. These gastric effects in the rat are the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid and are observed after long-term treatment in the rat with inhibitors of gastric acid secretion.

6. Pharmaceutical Particulars

6.1 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

6.2 Incompatibilities

None

6.3 Shelf-Life

24 months

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture

6.5 Nature and content of the container

An off white/light orange color, elongated shape, biconvex bilayered with brick red colour, film-coated bilayered tablet having a break line on one side of each tablet. Such 10 tablets are packed in an alu-alu pack, and such an alu-alu pack is packed in a printed carton with a packing insert.

Pack size: 1 X 10 Alu-Alu Pack

6.6 Special precautions for disposal and other handling

No Special Requirements.

7. Marketing Authorization Holder

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8. Marketing Authorization Number

CTD10031

9. Date of first authorization/renewal of the authorization

16/06/2023

10. Date of revision of the text

12/05/2025