Summary of Product Characteristics for Pharmaceutical Products

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
Naproxen Sodium BP.....500 mg
Excipients..... q.s
Colour: Red Oxide of Iron
For the full list of excipients see section 6.1

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.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 or substituted benzimidazoles.
- History of asthma, urticaria or allergic-type reactions induced by administration of acetylsalicylic acid or other NSAIDs (see section 4.4).
- Third trimester of pregnancy (see section 4.6).
- Severe hepatic impairment (e.g. Child-Pugh C).
- Severe heart failure.
- Severe renal impairment.
- Active peptic ulceration (see section 4.4, gastrointestinal effects *Naproxen*).
- Gastrointestinal bleeding, cerebrovascular bleeding or other bleeding disorders (see section 4.4, Haematological effects).
- XENOZ must not be used concomitantly with atazanavir and nelfinavir (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use General

The combination of XENOZ and NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided because of the cumulative risks of inducing serious NSAID-related adverse events. XENOZ can be used with low dose acetylsalicylic acid (see also section 4.5.).

Undesirable effects may be minimised by using the

lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

To prevent overtreatment, the prescriber should assess at clinically meaningful intervals based on the individual risks and depending on the characteristics and the severity of the treated underlying disease, whether sufficient pain control is possible with lower doses of NSAIDs as non-fixed combinations.

When total daily dose of 1000 mg of naproxen (500 mg twice daily) is not considered appropriate, alternative treatment with lower strength of naproxen or of other NSAIDs as non-fixed combination should be utilised, and in addition the need for continuation of the gastro protective treatment should be re-evaluated.

Risk-factors to develop NSAID related gastro-intestinal complications include high age, concomitant use of anticoagulants, corticosteroids, other NSAIDs including low-dose acetylsalicylic acid, debilitating cardiovascular disease, *Helicobacter pylori* infection, and a history of gastric and/or duodenal ulcers and upper gastrointestinal bleeding.

In patients with the following conditions, naproxen should only be used after a rigorous benefit-risk ratio:

- Inducible porphyries
- Systemic lupus erythematosus and mixed connective tissue disease, as rare cases of aseptic meningitis have been described in these patients.

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

XENOZ contains very low levels of methyl- and propyl parahydroxybenzoate, which may cause allergic reactions (possibly delayed). (See sections 2 and 6.1).

Elderly

Naproxen: Older people have an increased frequency of adverse reactions especially gastro-intestinal bleeding, and perforation, which may be fatal (see sections 4.2 and 5.2). The esomeprazole component of XENOZ decreased the incidence of ulcers in older people.

Gastrointestinal effects

Naproxen: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation with NSAIDs is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in older people. These patients should begin treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid, or other drugs likely to increase gastrointestinal risk (see below and 4.5). The esomeprazole component of XENOZ is a proton pump inhibitor.

Patients with a history of GI toxicity, particularly older people, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving NSAIDs with concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (for information on use of XENOZ with low-dose acetylsalicylic acid, see section 4.5).

Ulcer complications such as bleeding, perforation and obstruction were not studied in the XENOZ trials.

When GI bleeding or ulceration occurs in patients receiving XENOZ, the treatment should be withdrawn (see section 4.3).

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8 Undesirable effects).

Esomeprazole: In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as

treatment with esomeprazole magnesium may alleviate symptoms and delay diagnosis.

Dyspepsia could still occur despite the addition of esomeprazole to the combination tablet (see section 5.1).

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* (see section 5.1).

Esomeprazole, as all acid-blocking medicines, might reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors of reduced vitamin B12 absorption on long-term therapy.

Cardiovascular and cerebrovascular effects

Naproxen: Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of coxibs and some NSAIDs (particularly at high doses and in long-term treatment) may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke). Although data suggest that the use of naproxen (1000 mg daily) may be associated with a lower risk, some risk cannot be excluded.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with naproxen after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Renal effects

Naproxen: Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these

patients, administration of a NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, hypovolemia, heart failure, liver dysfunction, salt depletion, those taking diuretics, angiotensin converting enzyme (ACE) inhibitors, or angiotensin II receptor antagonists and older people.
Discontinuation of NSAID therapy is usually followed by recovery to
the pretreatment state (see also below, and sections 4.2 and 4.5).

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking esomeprazole and naproxen containing products and may occur at any point during Xenoz therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.

Xenoz should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

Use in patients with renal impairment

As naproxen and its metabolites are eliminated to a large extent (95%) by urinary excretion via glomerular filtration, it should be used with great caution in patients with impaired renal function and the monitoring of serum creatinine and/or creatinine clearance is advised in these patients. XENOZ is contraindicated in patients having a baseline creatinine clearance of less than 30 ml/minute (see section 4.3).

Haemodialysis does not decrease the plasma concentration of naproxen because of the high degree of protein binding.

Certain patients, specifically those whose renal blood flow is compromised, because of extracellular volume depletion, cirrhosis of the liver, sodium restriction, congestive heart failure, and pre-existing renal disease, should have renal function assessed before and during XENOZ therapy. Some older patients in whom impaired renal function may be expected, as well as patients using diuretics, ACE-inhibitors or angiotensin II receptor antagonists also fall within this category. A reduction in daily dosage should be considered to avoid the possibility of excessive

accumulation of naproxen metabolites in these patients.

Hepatic effects

Borderline elevations of one or more liver tests may occur in patients taking NSAIDs. Hepatic abnormalities may be the result of hypersensitivity rather than direct toxicity. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

Hepatorenal syndrome

The use of NSAIDs may be associated with acute renal failure in patients with severe hepato-cirrhosis. These patients frequently also have concomitant coagulopathy related to inadequate synthesis of clotting factors. Antiplatelet effects associated with naproxen could further increase risk of severe bleeding in these patients.

Haematological effects

Naproxen: Patients who have coagulation disorders or are receiving drug therapy that interferes with haemostasis should be carefully observed if naproxen-containing products are administered.Patients at high risk of bleeding and those on full anti-coagulation therapy (e.g. dicoumarol derivates) may be at increased risk of bleeding if given naproxen-containing products concurrently (see section 4.5).

Naproxen decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined.

When active and clinically significant bleeding from any source occurs in patients receiving XENOZ, the treatment should be withdrawn.

Eye effects

Naproxen: Because of adverse eye findings in animal studies with NSAIDs, it is recommended that an ophthalmic examination be carried out if any change or disturbance in vision occurs.

Dermatological effects

Naproxen: Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson

syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring within the first month of treatment in the majority of cases. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in patients taking NSAIDs. XENOZ should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Severe cutaneous adverse reactions (SCARs)

Esomeprazole: Severe cutaneous adverse reactions (SCARs) such as erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) which can be life-threatening or fatal, have been reported very rarely in association with esomeprazole treatment.

Patients should be advised of the signs and symptoms of the severe skin reaction EM/SJS/TEN/DRESS and should seek medical advice from their physician immediately when observing any indicative signs or symptoms. Xenoz should be discontinued immediately upon signs and symptoms of severe skin reactions and additional medical care/close monitoring should be provided as needed. Re-challenge should not be undertaken in patients with EM/SJS/TEN/DRESS.

*Esomeprazol*e: Proton pump inhibitors are associated with very infrequent cases of subacute cutaneous lupus erythematosus (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 XENOZ. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with otherproton pump inhibitors.

Anaphylactic (anaphylactoid) reactions

Naproxen: Hypersensitivity reactions may occur in susceptible individuals. Anaphylactic (anaphylactoid) reactions may occur both in patients with and without a history of hypersensitivity or exposure to acetylsalicylic acid, other NSAIDs or naproxen-containing products. They may also occur in

individuals with a history of angio-oedema, bronchospastic reactivity (e.g. asthma), rhinitis and nasal polyps.

Pre-existing asthma

Naproxen: The use of acetylsalicylic acid in patients with acetylsalicylic acid-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between acetylsalicylic acid and other NSAIDs has been reported in such acetylsalicylic acid-sensitive patients, XENOZ should not be administered to patients with this form of acetylsalicylic acid sensitivity (see section 4.3) and should be used with caution in patients with pre-existing asthma.

Inflammation

Naproxen: The anti-pyretic and anti-inflammatory activities of naproxen may reduce fever and other signs of inflammation, thereby diminishing their utility as diagnostic signs.

Female fertility

The use of XENOZ, as with any drug known to inhibit cyclooxygenase / prostaglandin synthesis, may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of XENOZ should be considered (see section 4.6).

Combination with other medicinal products:

Co-administration of atazanavir with proton pump inhibitors is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus loading) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100
mg of ritonavir; esomeprazole 20 mg should not be exceeded and therefore XENOZ must not be used concomitantly with atazanavir (see section 4.3).

Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole (see section 4.5). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of

esomeprazole and clopidogrel should be discouraged.

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like esomeprazole 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, hypomagnesaemia 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 before starting PPI treatment and periodically during treatment.

Bone fracture

Proton pump inhibitors, 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 proton pump inhibitors 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.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, XENOZ treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

XENOZ contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindications of concomitant use (see section

4.3)

Antiretroviral agents

Omeprazole, the racemate of D+S omeprazole (esomeprazole), has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these interactions are not always known.
Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75%decrease in AUC, Cmax and Cmin). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. Co-administration of omeprazole (40 mg qd) reduced mean nelfinavir AUC,
Cmax and Cmin by 36–39% and mean AUC, Cmax and Cmin for the pharmacologically active metabolite M8 was reduced by 75-92%.

For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs of which unchanged serum levels have been reported when given with omeprazole.

No interaction study has been performed with XENOZ and atazanavir. However, due to the similar pharmacodynamic and pharmacokinetic properties of omeprazole and esomeprazole, the concomitant use of atazanavir and nelfinavir with esomeprazole is not recommended and concomitant administration with XENOZ is contraindicated (see section 4.3).

Concomitant use with precaution

Other analgesics including cyclooxygenase-2 selective inhibitors

Concomitant use of two or more NSAIDs should be avoided as this may increase the risk of adverse effects, especially gastrointestinal ulcers and bleeding. The concomitant use of XENOZ with other NSAIDs, except for low-dose acetylsalicylic acid (≤

325 mg/day), is not recommended (see section 4.4).

Acetylsalicylic acid

XENOZ can be administered with low-dose acetylsalicylic acid (≤325 mg/day) therapy. In clinical trials, patients taking XENOZ in combination with low-dose acetylsalicylic acid did not have an increased occurrence of gastric ulcers compared to patients taking XENOZ alone (see section 5.1). However, the concurrent use of acetylsalicylic acid and XENOZ may still increase the risk of serious adverse events (see sections 4.4 and 4.8).

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.

Tacrolimus

As with all NSAIDs, there is a possible risk of nephrotoxicity when naproxen is co-administered with tacrolimus. Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus. During treatment with XENOZ, a reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

Ciclosporin

As with all NSAIDs, caution is advised when ciclosporin is co-administered because of the increased risk of nephrotoxicity.

Diuretics

Clinical studies, as well as postmarketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure, as well as to assure diuretic efficacy (see section 4.4).

Selective Serotonin Reuptake Inhibitors (SSRIs)

Concomitant use of NSAIDs, including COX-2 selective inhibitors, and SSRIs increases the risk of gastrointestinal bleeding (see section 4.4).

Corticosteroids

There is an increased risk of gastrointestinal bleeding when corticosteroids are combined with NSAIDs including COX–2 selective inhibitors. Caution should be used when NSAIDs are administered concomitantly with corticosteroids (see section 4.4).

ACE-inhibitors/Angiotensin II receptor antagonists

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors and angiotensin II receptor antagonists. NSAIDs may also increase the risk of renal impairment associated with the use of ACE-inhibitors or angiotensin II receptor antagonists. The combination of NSAIDs and ACE-inhibitors or angiotensin II receptor antagonists should be given with caution in patients who are older, volume-depleted, or with impaired renal function (see section 4.4).

Digoxin

NSAIDs may increase plasma cardiac glycoside levels when co-administered with cardiac glycosides such as digoxin.

Lithium

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. NSAIDs have been reported to reduce the tubular secretion of methotrexate in an animal model. This may indicate that both esomeprazole and naproxen could enhance the toxicity of methotrexate. The clinical relevance is likely to be greater in patients receiving high doses of methotrexate and in patients with renal dysfunction. Caution

should be used when XENOZ is administered concomitantly with methotrexate. In high-dose methotrexate administration a temporary withdrawal of XENOZ is recommended.

Sulphonylureas, Hydantoins

Naproxen is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other albumin-bound drugs such as sulphonylureas, and hydantoins. Patients simultaneously receiving naproxen and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic (PK)/pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%.

In a study in healthy subjects, there was a decreased exposure by almost 40% of the active metabolite of clopidogrel when a fixed dose combination of esomeprazole 20 mg and acetylsalicylic acid 81 mg was given with clopidogrel compared to clopidogrel alone. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were the same in both groups.

No clinical studies on the interaction between clopidogrel and the fixed dose combination of naproxen+esomeprazole (XENOZ) have been performed.

Inconsistent data on the clinical implications of a PK/PD interaction of esomeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of XENOZ and clopidogrel should be discouraged (see section 4.4).

Anti-coagulants and thrombocyte aggregation inhibitors

NSAIDs may enhance the effects of oral anti-coagulants (e.g. warfarin, dicoumarol) heparins and thrombocyte aggregation inhibitors (see section 4.4).

Concomitant administration of 40 mg esomeprazole to

warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R isomer of warfarin, the coagulation times were within the accepted range. However, from post marketed use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarine derivatives.

Beta receptor-blockers

Naproxen and other NSAIDs can reduce the antihypertensive effect of propranolol and other beta-blockers.

Probenecid

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

Drugs with gastric pH-dependent absorption

The gastric acid suppression during treatment with esomeprazole and other PPIs might decrease or increase the absorption of drugs with a gastric pH dependent absorption. Like with other drugs that decrease the intragastric acidity, the absorption of drugs such as ketoconazole, itraconazole, posaconazole and erlotinib can decrease while the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant use with posaconazole and erlotinib should be avoided. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Other Information Concerning Drug Interactions

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2-selective NSAID) did not identify any clinically relevant interaction.

As with other NSAIDs, concomitant administration of cholestyramine can delay the absorption of naproxen.

In healthy volunteers, concomitant administration of 40 mg esomeprazole resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life (t1/2) but no significant increase in peak

plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see also section 4.4).

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin and quinidine.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Esomeprazole is also metabolised by CYP3A4. The following have been observed in relation to these enzymes:

• Concomitant administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

• Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients.

• Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure.

• Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg twice daily), resulted in a doubling of the exposure (AUC) to esomeprazole.

Dose adjustment of esomeprazole is not required in any of these cases.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's Wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Omeprazole as well as esomeprazole act as inhibitors of CYP 2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

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.

Drug/Laboratory Test Interaction

Naproxen may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined.

The administration of naproxen may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-di-nitrobenzene used in this assay. Although 17-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that therapy with naproxen be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.

Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).

4.6 Pregnancy and Lactation Pregnancy

Naproxen:

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. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. 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 (see section 5.3).

In women attempting to conceive or during the first and second trimester of pregnancy, XENOZ should not be given unless the potential benefit to the patient outweighs the potential risk to the foetus.

From the 20th week of pregnancy onward, XENOZ use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation.

Therefore, if naproxen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and the duration of treatment as short as possible.

Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to XENOZ for several days from gestational week 20 onward. XENOZ should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- 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.

Consequently, XENOZ is contraindicated during the third trimester of pregnancy (see section 4.3).

Esomeprazole:

There are limited amount of data from the use of esomeprazole in pregnant women. With the racemic mixture omeprazole, data on a larger number of exposed pregnancies stemming from epidemiological studies indicate no malformative nor foetotoxic effects. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/foetal development. Animal studies with the racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development.

Breast-feeding

Naproxen is excreted in low quantities in human milk. It is unknown whether esomeprazole is excreted in human milk. A published case report on the racemic mixture omeprazole indicated excretion of

low quantities in the human breast milk (weight adjusted dose < 7%). XENOZ should not be used during breastfeeding.

Fertility

The use of NSAIDs like naproxen may impair female fertility. The use of XENOZ is not recommended in women attempting to conceive (see section 4.4).

4.6 Effects on ability to drive and use machines

XENOZ has minor influence on the ability to drive and use machines; based on that some of the adverse effects (e.g. dizziness) reported following the use of XENOZ may reduce the ability to react.

4.7 Undesirable effects

Summary of safety profile

Immediate release esomeprazole has been included in the tablet formulation to decrease the incidence of gastrointestinal side effects from naproxen.
XENOZ has been shown to significantly decrease the occurrence of gastric ulcers and NSAID associated upper gastrointestinal adverse events compared to naproxen alone (see section 5.1).

No new safety findings were identified during XENOZ treatment in the overall study population (n=1157) compared to the well-established safety profiles of the individual active substances naproxen and esomeprazole.

Tabulated summary of adverse reactions

Adverse reactions are classified according to frequency and System Organ Class. Frequency categories are defined according to the following convention: Very common (≥ 1/10), 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).

XENOZ

The following adverse experiences have been reported in patients taking XENOZ 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			asthma, bronchospasm, dyspnea	

disorders				
Gastrointesti n al disorders	dyspeps i a	abdominal pain, constipation, diarrhoea, esophagitis, flatulence, gastric/duod e nal ulcers*, gastritis, nausea, vomiting	dry mouth, eructation, gastrointesti n al bleeding, stomatitis	glossitis, hematemesi s, rectal bleeding
Skin and subcutaneou s tissue disorders		skin rashes	dermatitis, hyperhidrosi s, pruritus, urticaria	alopecia, ecchymoses

Musculoskele t al and connective tissue disorders		arthralgia	myalgia	
Renal and urinary disorders				proteinuria, renal failure
Reproductiv e system and breast disorders				menstrual disorder
General disorders and administrati o n site disorders		oedema	asthenia, fatigue, pyrexia	
Investigation s			abnormal liver function tests, raised serum creatinine	

*as detected by scheduled routine endoscopy

NaproxenThe following adverse experiences have been reported in patients taking naproxen during clinical trials and through postmarketing reports.

	Uncommon	**Uncommon/Rare**
Infections and infestations		aseptic meningiti s, infection, sepsis

Blood and lymphatic system disorders		agranulocytosis, aplastic anemia, eosinophilia, granulocytopenia, hemolytic anemia, leucopenia, lymphadenopathy, pancytopenia, thrombocytopenia
Immune system disorders		anaphylactic reactions, anaphylactoid reactions, hypersensitivity reactions
Metabolism and nutrition disorders		appetite disorder, fluid retention, hyperglycemia, hyperkalemia, hyperuricemia, hypoglycemia, weight changes
Psychiatric disorders	depression, insomnia	agitation, anxiety, confusion, dream abnormalities, hallucinations, nervousness
Nervous system disorders	dizziness, drowsiness, headache, lightheadedness, vertigo	cognitive dysfunction, coma, convulsions, inability to concentrate, optic neuritis, paresthesia, syncope, tremor

Eye disorders	visual disturbances	blurred vision, conjunctivitis, corneal opacity, papilloedema, papillitis

Ear and labyrinth disorders	tinnitus, hearing disturbances	hearing impairment
Cardiac disorders	palpitations	arrhythmia, congestive heart failure, myocardial infarction, tachycardia
Vascular disorders		hypertension, hypotension, vasculitis
Respiratory, thoracic and mediastinal disorders	dyspnea	asthma, bronchospasm, eosinophilic pneumonitis, pneumonia, pulmonary edema, respiratory depression
Gastrointestinal disorders	dyspepsia, abdominal pain, nausea, vomiting, diarrhoea, constipation, heartburn, peptic ulcers, stomatitis	dry mouth, esophagitis, gastric ulcers, gastritis, glossitis, eructation, flatulence, gastric/duodenal ulcers, gastrointestinal bleeding and/or perforation, melena, hematemesis, pancreatitis, colitis, exacerbation of inflammatory bowel disease (ulcerative colitis, Crohn's disease), nonpeptic gastrointestinal ulceration, rectal bleeding, ulcerative stomatitis

Hepatobiliary disorders		cholestasis, hepatitis, jaundice, liver failure
Skin and subcutaneous tissue disorders	pruritus, ecchymoses, purpura, skin rashes	alopecia, exanthema,urticaria , bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN), erythema multiforme,
		erythema nodosum, fixed drug eruption, lichen planus, systemic lupus erythematosus, photosensitive dermatitis, photosensitivity reactions, including rare cases resembling porphyria cutanea tarda (pseudoporphyria), exfoliative dermatitis, angioneurotic edema, pustular reaction
Musculoskeletal and connective tissue disorders		muscle weakness, myalgia

Renal and urinary disorders		glomerular nephritis, hematuria, tubulointerstitial nephritis (with possible progression to renal failure), nephrotic syndrome, oliguria/polyuria , proteinuria, renal failure, renal papillary necrosis, tubular necrosis
Reproductive system and breast disorders		infertility, menstrual disorder
General disorders and administration site disorders	fatigue, oedema, sweating, thirst	asthenia, malaise, pyrexia
Investigations		abnormal liver function tests, increased bleeding time, raised serum creatinine

Esomeprazole:The following adverse drug reactions have been identified or suspected in the clinical trials programme for enteric-coated esomeprazole and/or from post marketing use. None were found to be dose-related.

	Common	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders			leukopenia, thrombocytopenia	agranulocytosis, pancytopenia	

Immune system disorders			hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/ shock		
Metabolism and nutrition disorders		peripheral oedema	hyponatraemia		hypomagnesaemia, severe hypomagnesaemia may result in hypocalcaemia; hypomagnesaemia may also be associated with hypokalaemia.
Psychiatric disorders		insomnia	agitation, confusion, depression	aggression, hallucinations	
Nervous system disorders	headache	dizziness, paraes	taste disturbance		

		t hesia,			
		somnol e nce			
Eye disorde r			blurred vision		
Ear and labyrin th disorde rs		vertigo			
Respira t o ry, thoraci c and medias ti n al disorde rs			bronchos p asm		
Gastroi nt estinal disorders	abdomin al pain, diarrho ea, flatulen ce, nausea/ vo miting, constipat io n, fundic gland polyps (benign)	dry mouth	stomatit is, gastroint es tinal candidia si s	microsc op ic colitis	

Hepatobiliary disorders		increased liver enzymes	hepatitis with or without jaundice	hepatic failure, hepatic encephalopathy in patients with pre-existing liver disease	

Musculoskeletal and connective tissue disorders		fracture of the hip, wrist or spine (see section 4.4)	arthralgia, myalgia	muscular weakness	
Renal and urinary disorders				Tubulointerstitial nephritis (with possible progression to renal failure)	
Reproductive system and breast disorders				gynaecomastia	
General disorders and administration site disorders			malaise, increased sweating		

Description of selected adverse reactions

Naproxen

Clinical trial and epidemiological data suggest that use of coxibs and some NSAIDs (particularly at high doses and in long-term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Although data suggest that the use of naproxen (1000 mg daily) may be associated with a lower risk, some risk cannot be excluded (see section 4.4).

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in older people, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4 - Special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed.

XENOZ has been developed with esomeprazole to decrease the incidence of gastrointestinal side effects from naproxen and has been shown to significantly decrease the occurrence of gastric and/or duodenal ulcers and NSAID associated upper gastrointestinal adverse events compared to naproxen alone.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the National Regulatory Authority.

4.9 Overdose

There is no clinical data on overdose with XENOZ.Any effects of an overdose with XENOZ would be expected to primarily reflect the effects of an overdose with naproxen.

Symptoms

Related to naproxen overdose

Significant naproxen overdosage may be characterized by lethargy, dizziness, drowsiness, epigastric pain, abdominal discomfort, heartburn, indigestion, nausea, transient alterations in liver function, hypoprothrombinemia, renal dysfunction, metabolic acidosis, apnea, disorientation or vomiting.

Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression, and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose. A few patients have experienced convulsions, but it is not clear whether or not these were drug-related. It is not known what dose of the drug would be life-threatening.

Related to esomeprazole overdose

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 esomeprazole were uneventful.

Management

Related to naproxen

Patients should be managed by symptomatic and supportive care following a NSAID overdose, particularly with respect to GI effects and renal damage.
There are no specific antidotes.

Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine or hemoperfusion may not be useful due to high protein binding.

Related to esomeprazole

No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

5 Pharmacological properties

5.1 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.

5.2 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 ofesomeprazole 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.

5.3 Preclinical safety data

None

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

2 years

6.4 Special Precautions for storage

Store below 30°C. Protect from light and moisture

6.5 Nature and Content 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.

6.6 Special precautions for disposal and other handling

No Special Requirements.

7 Marketing Authorization Holder

SALUD CARE (I) PRIVATE LIMITED

435, Kishanpur Jamalpur, Opp. Pharma College of Roorkee, Roorkee- 247 661Haridwar, Uttarakhand, INDIA

8 Market Authorization Number

3139

9 Date of first authorization/renewal of the authorization

2023 June 22

10 Date of revision of the text

2028 June 22