Espra-X® 500/20 mg Tablet

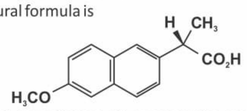
ایسپرا۔ایکس

(NAPROXEN + ESOMEPRAZOLE)

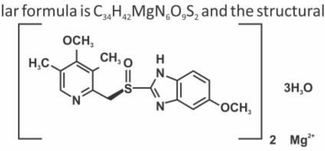
Description

Espra-X is indicated in adults for the symptomatic treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, in patients who are at risk for developing non-steroidal anti-inflammatory drugs (NSAIDs) associated with gastric or duodenal ulcers and where treatment with lower doses of naproxen with other NSAIDs is not considered sufficient.

Naproxen is an NSAID with analgesic and antipyretic properties. The mechanism of action of the naproxen, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition. Its molecular formula is $C_{14}H_{14}O_3$ and the structural formula is



Esomeprazole is the *S*-enantiomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. Esomeprazole, a weak base is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+K^+-ATPase – the acid pump and inhibits both basal and stimulated acid secretion. Its molecular formula is $C_{34}H_{42}MgN_6O_5S_2$ and the structural formula is



Composition

Each film coated, delayed release tablet contains:

Naproxen ..... 500 mg.

(Enteric coated core)

Esomeprazole as magnesium trihydrate ..... 20 mg.

(Immediate release coat)

Product Specs.: Innovator

WARNING: CARDIOVASCULAR AND GASTROINTESTINAL RISKS

See full prescribing information for complete boxed warning

Cardiovascular Risk

- Naproxen, a component of Espra-X, may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risks factors for cardiovascular disease may be at greater risk.
- Espra-X is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal Risk

- **NSAIDs,** including naproxen, a component of Espra-X, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal (GI) events.

Pharmacodynamic Properties

Pharmacotherapeutic group: naproxen and esomeprazole ATC code: M01AE52

Mechanism of action

Espra-X has been developed as a sequential-delivery tablet formulation combining an immediate release esomeprazole magnesium layer and an enteric coated delayed-release naproxen core. As a result, esomeprazole is released in the stomach prior to the dissolution of naproxen in the small intestine. The enteric coating prevents naproxen release at pH levels below 5 providing protection against possible local gastric toxicity of naproxen.

Due to the delayed-release of naproxen, Espra-X is not intended for, and has not been studied in acute pain.

Naproxen is an NSAID with analgesic and antipyretic properties. The mechanism of action of the naproxen anion, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

Esomeprazole is the *S*-enantiomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action.

Pharmacodynamic effects

Effect on gastric acid secretion

An optimal effect (maintenance of high gastric pH) was achieved with Espra-X formulation containing 20 mg of esomeprazole. After 9 days of dosing twice daily with Espra-X, intragastric pH above 4 was maintained for a mean time of 17.1 hours (SD 3.1) in healthy volunteers. The corresponding value for Esomeprazole 20mg was 13.6 hours (SD 2.4).

Other effects related to acid inhibition

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also, CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumors. Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

During long-term treatment with antisecretory drugs, gastric glandular cysts have been reported to occur at a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

Pediatric Population

The European Medicines Agency has waived the obligation to submit the results of studies with Espra-X.

Pharmacokinetic properties

Absorption

Naproxen

After single dose application, the time to peak plasma concentration is achieved after 3 to 5 hours, however, food intake results in further delay up to 8 hours or more. At steady state following administration of Espra-X twice daily, peak plasma concentrations of naproxen are reached within a median time of 3 hours following both the morning and the evening dose.

Bioequivalence between Espra-X and enteric-coated naproxen, based on both area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}) of naproxen, has been demonstrated.

Naproxen is rapidly and completely absorbed from the gastrointestinal tract with an *in vivo* bioavailability of 95%.

Steady-state levels of naproxen are reached in 4 to 5 days.

Esomeprazole

Following administration of Espra-X twice daily, esomeprazole is rapidly absorbed with peak plasma concentration reached within a median time of 0.5-0.75 hours following the morning and evening dose on both the first day of administration and at steady state. After repeated b.i.d dosing of Espra-X, the C_{max} was 2-3 times higher, and the AUC 4-5 times higher, as compared to the first day of dosing. This is probably partly a result of an increased absorption due to the pharmacodynamic effect of esomeprazole with increased intragastric pH, leading to reduced acid degradation of esomeprazole in the stomach. A decrease of first pass metabolism and systemic clearance of esomeprazole with repeated dosing also contributes to the higher plasma concentrations at steady state.

Concomitant administration with food

Administration of Espra-X together with food does not affect the extent of absorption of naproxen but significantly delays the absorption by about 8 hours and decreases peak plasma concentration by about 12%.

Administration of Espra-X together with food does not delay the absorption of esomeprazole but significantly reduces the extent of absorption, resulting in 52% and 75% reductions of area under the plasma concentration versus time curve and peak plasma concentration, respectively.

Administration of Espra-X 30 minutes before food intake has only minimal or no effect on the extent and time to absorption of naproxen and has no significant effect on the rate or extent of esomeprazole absorption compared to administration under fasted conditions

Distribution

Naproxen

Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels naproxen is greater than 99% albumin-bound. 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.

Esomeprazole

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% plasma protein bound.

Elimination

Naproxen

Following administration of Espra-X twice daily, the mean elimination half-life for naproxen is approximately 9 hours and 15 hours following the morning and evening dose, respectively, 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.

Esomeprazole

Following administration of Espra-X twice daily, the mean elimination half-life for 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).

Special populations

Renal impairment

The pharmacokinetics of Espra-X has not been determined in patients with renal impairment.

Naproxen: Naproxen pharmacokinetics has not been determined in subjects with renal impairment.

Given that naproxen, its metabolites and conjugates are primarily excreted by the kidney, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency. Elimination of naproxen is decreased in patients with severe renal impairment. Espra-X is contraindicated for use in patients with severe renal impairment (creatinine clearance < 30 ml/min)

Esomeprazole: No studies have been performed with esomeprazole in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Hepatic impairment

The pharmacokinetics of Espra-X has not been determined in patients with impaired hepatic function.

Naproxen: The pharmacokinetics of naproxen has not been determined in subjects with hepatic impairment.

Chronic alcoholic liver disease and probably also other forms of cirrhosis reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. The implication of this finding for the naproxen component of Espra-X dosing is unknown but it is prudent to use the lowest effective dose.

Esomeprazole: The metabolism of esomeprazole in patients with mild to moderate hepatic impairment may be impaired. The metabolic rate is decreased in patients with severe hepatic impairment resulting in a doubling of the area under the plasma concentration-time curve of esomeprazole.

Patients with severe hepatic insufficiency should not receive Espra-X

Special warnings and precautions for use

Espra-X is not recommended for use in children or adolescents aged 18 years or younger.

General

The combination of Espra-X and NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided because of the cumulative risks of inducing serious NSAID-related adverse events. Espra-X can be used with low dose acetylsalicylic acid.

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 utilized, and in addition the need for continuation of the gastro protective treatment should be re-evaluated.

Elderly

Naproxen: Older people have an increased frequency of adverse reactions especially gastro-intestinal bleeding, and perforation, which may be fatal. The esomeprazole component of Espra-X 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 any time during treatment, with or without warning symptoms or a previous history of serious GI events.

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. The esomeprazole component of Espra-X is a proton pump inhibitor.

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

Esomeprazole: In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, hematemesis 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.

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*

Esomeprazole, as all acid-blocking medicines, might reduce the absorption of vitamin B_{12} (cyanocobalamin) due to hypo or achlorhydria. This should be considered in patients with reduced body stores or risk factors of reduced vitamin B_{12} 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.

Female fertility

The use of Espra-X, 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 Espra-X should be considered.

Combination with other medicinal products:

Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with drugs metabolized through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole. 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.

Interference with laboratory tests

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

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

Contraindications

History of asthma, urticaria or allergic-type reactions induced by administration of acetylsalicylic acid or other NSAIDs.

Third trimester of pregnancy

Severe hepatic impairment (e.g. Child-Pugh C).

Severe heart failure.

Severe renal impairment.

Active peptic ulceration.

Gastrointestinal bleeding, cerebrovascular bleeding or other bleeding disorders Hematological effects).

Espra-X must not be used concomitantly with atazanavir and nelfinavir

Therapeutic Indications

Espra-X is indicated in

- Osteoarthritis
- Rheumatoid Arthritis
- Low Back Pain
- Post-Operative Pain
- Acute and Chronic Pain

Espra-X with food and drink

Do not take Espra-X with food as this may reduce and/or delay the effect of Espra-X. Take your tablets at least 30 minutes before you have a meal.

Fertility, pregnancy and lactation

Do not take Espra-X if you are in the last 3 months of pregnancy.

Talk to your doctor before taking this medicine if you are in the first or second trimester of pregnancy.

Do not breast-feed if you are taking Espra-X. This is because small amounts may pass into the mothers' milk. If you are planning to breast-feed you should not take Espra-X.

Ask your doctor or pharmacist for advice before taking any medicine if you are pregnant, might become pregnant or are breast-feeding. Espra-X may make it more difficult to become pregnant.

You should inform your doctor if you are planning to become pregnant or if you have problems to become pregnant.

Overdose

There is no clinical data on overdose with Espra-X.

Any effects of an overdose with Espra-X 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.

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.

INSTRUCTIONS:

- Store below 30ºC.
- Protect from heat, sunlight and moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

ہدایات:

۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

گرمی، دھوپ اور نمی سے بچائیں۔

بچوں کی پہنچ سے دور رکھیں۔

صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

PRESENTATION:

Espra-X 500/20 mg Tablet : Pack of 4 x 7 tablets.

Manufactured by:
DYSON Research Laboratories (Pvt) LTD.
28th-KM Ferozepur Road, Lahore, Pakistan.

FOR FURTHER INFORMATIONS PLEASE CONTACT:

Manufactured for:
CCL Pharmaceuticals (Pvt.) Ltd.
62 Industrial Estate, Kot Lakhpat, Lahore, Pakistan.