Axesom®
(Esomeprazole)

Highnoon

COMPOSITION
Axesom 20mg Capsule: Each capsule contains:
Enteric coated pellets of Esomeprazole magnesium trihydrate equivalent to Esomeprazole 20mg
Axesom 40mg Capsule: Each capsule contains:
Enteric coated pellets of Esomeprazole magnesium trihydrate equivalent to Esomeprazole 40mg

DESCRIPTION
The active ingredient in Axesom is Esomeprazole Magnesium trihydrate. Esomeprazole is a proton pump inhibitor and is the S - isomer of Omeprazole, which is a mixture of S - and R - isomers.

MECHANISM OF ACTION
Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H+/K+ ATPase in the gastric parietal cells. The S - and R - isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity.

PHARMACOKINETICS
Esomeprazole is rapidly absorbed after oral doses and peak plasma level occurs at about 1 to 2 hours. Bioavailability of esomeprazole increases on repeated dosage to about 68% and 89% for doses of 20mg and 40mg respectively. Food delays and decreases the absorption of esomeprazole, but this does not change its effect on intragastric acidity. It should be taken at least one hour before meals. It is acid labile. Esomeprazole is 97% bound to plasma proteins and is extensively metabolized in the liver by the cytochrome P450 isoenzyme CYP2C19 to hydroxyl and desmethyl metabolites, which have no effect on gastric acid secretion. The remainder is metabolized by the cytochrome P450 isoenzyme CYP3A4 to esomeprazole sulfone. With repeated dosage, there is a decrease in first-pass metabolism and systemic clearance, probably caused by an inhibition of the CYP2C19 isoenzyme. However, there is no accumulation during once daily dose. The plasma elimination half-life of esomeprazole is approximately 1.3 hours. Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, and the remainder in the feces.

INDICATIONS AND USAGE
It is indicated in the following conditions:

- Treatment of Gastroesophageal Reflux Disease (GERD)
  - o Healing of erosive esophagitis
  - o Maintenance of healing of erosive esophagitis
  - o Symptomatic gastroesophageal reflux disease (in the absence of esophagitis)
- NSAID - associated ulceration
  - o NSAID associated gastric ulcer
  - o Prophylaxis of NSAID-associated gastric ulcer in patients with an increased risk of gastroduodenal complications who require continuous NSAID treatment
  - o Prophylaxis of NSAID-associated gastric or duodenal ulcer
- Zollinger-Ellison Syndrome
- H. Pylori eradication to reduce the risk of duodenal ulcer recurrence

DOSAGE AND ADMINISTRATION
Treatment of Gastroesophageal Reflux Disease (GERD)

- o Healing of erosive esophagitis
  - In adults for the short-term treatment; 20mg or 40mg once daily for 4 to 8 weeks in the healing and symptomatic resolution of confirmed erosive esophagitis. For those patients who have not healed after 4 to 8 weeks of treatment, an additional 4 to 8 week course may be considered.
  - In children 12 to 17 years of age; a dose of 20mg or 40mg once daily for 4 to 8 weeks.
  - In children 1 to 11 years of age (body weight less than 20kg); 10mg once daily for 8 weeks.
  - In children 1 to 11 years of age (body weight greater than or equal to 20 kg); 10mg or 20mg once daily for 8 weeks.
  - In children 1 month to less than 1 year of age (body weight 3 kg to 5 kg) due to acid-mediated GERD; 2.5mg once daily for up to 6 weeks.
  - In children 1 month to less than 1 year of age (body weight more than 5 kg to 7.5 kg) due to acid-mediated GERD; 5mg once daily for up to 6 weeks.
- o Maintenance of healing of erosive esophagitis
  - In adult 20mg once daily, do not extend beyond six months.
- o Symptomatic gastroesophageal reflux disease (in the absence of esophagitis)
  - In adult 20mg once daily for 4 weeks, if symptoms not resolved completely an additional 4 weeks treatment may be considered.
  - In children 12 to 17 years of age; a dose of 20mg once daily for 4 weeks.
  - In children 1 to 11 years of age; 10mg once daily for up to 8 weeks.

NSAID - associated ulceration

- o NSAID associated gastric ulcer
  - In adult; 20mg once daily for 4 to 8 weeks.
- o Prophylaxis of NSAID-associated gastric ulcer in patients with an increased risk of gastroduodenal complications who require continuous NSAID treatment

Zollinger - Ellison Syndrome

- o In adult; 20mg or 40mg once daily for up to 6 months.
  - Initially 40mg twice daily, adjusted according to response; usual dose 80mg to 160mg daily, daily doses above 80mg should be given in 2 divided doses.

H. Pylori eradication to reduce the risk of duodenal ulcer recurrence.

- In triple therapy combination; a 40mg once daily (for 10 days) along with amoxicillin 1000mg twice daily (for 10 days) and clarithromycin 500mg twice daily (for 10 days).

CONTRAINDICATIONS
- It is contraindicated in patients with known hypersensitivity to PPI or any of the other constituents of the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis and urticaria.
- Proton pump inhibitors (PPIs), including esomeprazole, are contraindicated in patients receiving rilpivirine containing products.

ADVERSE REACTIONS
The reported adverse events are: acute interstitial nephritis, Clostridium Difficile-Associated Diarrhea, bone fracture, Cutaneous and Systemic Lupus Erythematosus, cyanocobalamin (Vitamin B-12) deficiency, hypomagnesemia, fundic gland polyps, headache, diarrhea, flatulence, nausea, abdominal pain, constipation, dry mouth, abdomen enlarged, allergic reaction, asthenia, back pain, chest pain, substernal chest pain, facial edema, peripheral edema, hot flushes, fatigue, fever, flu-like disorder, generalized edema, leg edema, malaise, pain, rigors, flushing, hypertension, tachycardia, bowel irregularity, dyspepsia, dysphagia, dysplasia GI, epigastric pain, eructation, esophageal disorder, frequent stools, gastroenteritis, GI hemorrhage, hiccup, melena, mouth disorder, pharynx disorder, rectal disorder, serum gastrin increase, tongue disorder, tongue edema, ulcerative stomatitis, vomiting, earache, tinnitus, anemia, anemia hypochromic, leukocytosis, thrombocytopenia, leukopenia, bilirubinemia, hepatic function abnormal, epistaxis, cervical lymphadenopathy, SGOT increased, SGPT increased, glycosuria, hyperuricemia, hyponatremia, increased alkaline phosphatase, thirst, weight increase, weight decrease, arthralgia, arthritis aggravated, arthropathy, cramps, fibromyalgia syndrome, hernia, polymyalgia rheumatica, anorexia, apathy, appetite increased, confusion, depression, dizziness, hypertonia, nervousness, hypoesthesia, impotence, insomnia, migraine, paresthesia, sleep disorder, somnolence, tremor, vertigo, visual field defect, dysmenorrhea, menstrual disorder, vaginitis, asthma, coughing, dyspnea, larynx edema, pharyngitis, rhinitis, sinusitis, acne, angioedema, dermatitis, pruritus, pruritus ani, rash, rash erythematous, rash maculo-papular, skin inflammation, sweating increased, urticaria, otitis media, parosmia, taste loss, taste perversion, abnormal urine, albuminuria, cystitis, dysuria, fungal infection, hematuria, micturition frequency, moniliasis, genital moniliasis, polyuria, conjunctivitis, abnormal vision, increased creatinine, increase uric acid, increase total bilirubin, increase alkaline phosphatase, increase ALT, increase AST, increase hemoglobin, increase white blood cell count, increase platelets, increase serum gastrin, increase potassium, increase sodium, increase thyroxine and thyroid stimulating hormone, decrease hemoglobin, decrease white blood cell count, decrease platelets, decrease potassium, decrease sodium, decrease thyroxine, duodenitis, esophagitis, esophageal stricture, esophageal ulceration, esophageal varices, gastric ulcer, gastritis, hernia, benign polyps or nodules, Barrett's esophagus, mucosal discoloration, somnolence, regurgitation and tachypnea.
The additional reported adverse events are: agranulocytosis, pancytopenia, pancreatitis, microscopic colitis, hepatic failure, hepatitis with or without jaundice, anaphylactic reaction / shock, GI candidiasis, hypokalemia, muscular weakness, myalgia, hepatic encephalopathy, aggression, agitation, depression, hallucination, gynecomastia, bronchospasm, alopecia, erythema multiforme, hyperhidrosis, photosensitivity, Stevens-Johnson syndrome and toxic epidermal necrolysis.

PRECAUTIONS AND WARNINGS
- Before giving PPI to patient with gastric ulcers the possibility of the malignancy should be excluded since these drugs may mask symptoms and delay diagnosis. Consider additional follow-up and diagnostic testing in adult patients who have a suboptimal response or an early symptomatic relapse after completing treatment with a PPI. In older patients, also consider an endoscopy.
- PPI therapy like esomeprazole may be associated with an increased risk of Clostridium Difficile-Associated Diarrhoea, especially in hospitalized patients. This diagnosis should be considered for diarrhoea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Clostridium Difficile-Associated Diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents.
- Cutaneous Lupus Erythematosus (CLE) and Systemic Lupus Erythematosus (SLE) have been reported in patients taking PPIs, including esomeprazole. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE. The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement. Systemic Lupus Erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported. Avoid administration of PPI for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving esomeprazole discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g., ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.
- PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPI users who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.
- Avoid concomitant use of PPI (esomeprazole) with clopidogrel. Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is entirely due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by use with concomitant medications, such as esomeprazole, that inhibit CYP2C19 activity.
- Proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines.
- Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.
- Acute interstitial nephritis has been observed in patients taking PPIs. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue esomeprazole if acute interstitial nephritis develops.
- Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.
- Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop esomeprazole treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high.
- Concomitant use of PPIs with methotrexate (primarily at high dose may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may be considered in some patients.
- Drugs which induce CYP2C19 or CYP3A4 (such as St. John's Wort or rifampin) can substantially decrease esomeprazole concentrations. Avoid concomitant use of esomeprazole with St. John's Wort or rifampin.
- High doses of PPI over a prolong period of treatment in gastric tumours may lead to carcinoid like tumours of the gastric mucosa.
- In Helicobacter Infection treatment with PPI may cause false negative results in the urea breath test for H. Pylori infection.
- No dosage adjustment of esomeprazole is considered necessary for patient with mild to moderate hepatic impairment (Child - Pugh) classes A & B respectively. In severe hepatic impairment (Child - Pugh) Class C, a daily dose of 20 mg orally should not be exceeded.
- Although no dosage adjustment is considered necessary in patients with renal impairment, but a caution should be exercised with severe renal impairment, as experience in these is limited.
- Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with the use of proton pump inhibitors. Discontinue esomeprazole at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

DRUG INTERACTIONS
- Concomitant use of ilpivirine atazanavir and nelfinavir with proton pump inhibitors is not recommended. Co-administration of atazanavir with proton pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and may result in a loss of therapeutic effect and the development of drug resistance. Co-administration of saquinavir with proton pump inhibitors is expected to increase saquinavir concentrations, which may increase toxicity and require dose reduction. Omeprazole, of which esomeprazole is an enantiomer, 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. Some antiretroviral drugs, such as atazanavir and nelfinavir, decreased serum levels when given together with omeprazole. Concomitant administration with omeprazole and drugs such as atazanavir and nelfinavir is therefore not recommended. Other antiretroviral drugs, such as saquinavir, elevated serum levels. Clinical and laboratory monitoring for saquinavir toxicity is recommended during concurrent use with esomeprazole. Dose reduction of saquinavir should be considered from the safety perspective for individual patients.
- Due to its effects on gastric acid secretion, esomeprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Like with other drugs that decrease the intragastric acidity, the absorption of drugs such as ketoconazole, atazanavir, iron salts, erlotinib, and mycophenolate mofetil (MMF) can decrease, while the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Esomeprazole is an enantiomer of omeprazole. Co-administration of digoxin with esomeprazole is expected to increase the systemic exposure of digoxin. Therefore, patients may need to be monitored when digoxin is taken concomitantly with esomeprazole. Co-administration of omeprazole in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. Use esomeprazole with caution in transplant patients receiving MMF.
- Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4. Esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1, and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Esomeprazole does not have any clinically significant interactions with phenytoin, warfarin, quinidine, clarithromycin, or amoxicillin. Changes in prothrombin measures have been received among patients on concomitant warfarin and esomeprazole therapy. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time. Esomeprazole may potentially interfere with CYP2C19, the major esomeprazole metabolizing enzyme. Co-administration of esomeprazole and diazepam, a CYP2C19 substrate, resulted in a decrease in clearance of diazepam.
- Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of esomeprazole results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. Avoid concomitant administration of esomeprazole with clopidogrel. When using esomeprazole, consider use of alternative anti-platelet therapy.
- Omeprazole acts as an inhibitor of CYP2C19. Co-administration of cilostazol with esomeprazole is expected to increase concentrations of cilostazol and its active metabolite. Consider the reducing dose of cilostazol to 50 mg twice daily.
- 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. Dose adjustment of esomeprazole is not normally required. However, in patients with Zollinger-Ellison's Syndrome, dose adjustment may be considered.
- Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampin) may lead to decreased esomeprazole serum levels. Omeprazole, of which esomeprazole is an enantiomer, has been reported to interact with St. John's Wort, an inducer of CYP3A4. Avoid concomitant use of St. John's Wort or rifampin and ritonavir containing products with esomeprazole.
- Drug-induced decrease in gastric acidity results in enterochromaffin-like cell hyperplasia and increased Chromogranin A levels which may interfere with investigations for neuroendocrine tumours.
- Concomitant administration of esomeprazole and tacrolimus may increase the serum levels of tacrolimus.
- Co-administration of esomeprazole, clarithromycin, and amoxicillin has resulted in increases in the plasma levels of esomeprazole and 14-hydroxyclarithromycin. Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions due to drug interactions. Because of these drug interactions, clarithromycin is contraindicated for co-administration with certain drugs.
- Concomitant administration of PPIs and methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxy methotrexate. A temporary withdrawal of esomeprazole may be considered in some patients receiving high-dose methotrexate.
- Increased exposure of citalopram leading to an increased risk of QT prolongation. Limit the dose of citalopram to a maximum of 20 mg per day.
- Concomitant administration of clarithromycin with other drugs can lead to serious adverse reactions, including potentially fatal arrhythmias, and are contraindicated.

USE IN SPECIFIC POPULATIONS
There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Esomeprazole is the S-isomer of omeprazole. Esomeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Esomeprazole is likely present in human milk. Esomeprazole is the S-isomer of omeprazole and limited data indicate that omeprazole may be present in human milk. There are no clinical data on the effects of esomeprazole on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for esomeprazole and any potential adverse effects on the breastfed infant from esomeprazole or from the underlying maternal condition.

Paediatric Use
The safety and effectiveness of esomeprazole have been established in paediatric patients 1 to 17 years of age for short-term treatment (up to eight weeks) of GERD. The safety and effectiveness of esomeprazole have been established in paediatric patients 1 month to less than 1 year for short-term treatment (up to 6 weeks) of erosive esophagitis due to acid-mediated GERD. However, the safety and effectiveness of esomeprazole have not been established in patients less than 1 month of age.

Geriatric Use
No overall differences in safety & efficacy were observed between the elderly & younger individuals, and other reported clinical experience has not identified differences in responses between the elderly & younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Insufficiency
In patients with mild to moderate liver impairment (Child-Pugh Classes A and B), no dosage adjustment is necessary. In patients with severe hepatic impairment (Child-Pugh Class C) exposure to esomeprazole substantially increased compared to healthy subjects. Dosage modification of esomeprazole is recommended for patients with severe hepatic impairment for the healing of erosive esophagitis, risk reduction of NSAID-associated gastric ulcer, H. pylori eradication to reduce the risk of duodenal ulcer recurrence, and pathological hypersecretory conditions including Zollinger-Ellison Syndrome.

OVERDOSAGE
The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia, and intermittent clonic convulsions. Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache and dry mouth. 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. As with the management of any overdose, the possibility of multiple drug ingestion should be considered.

DOSAGE AND INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

PRESENTATION
Axesom 20mg Capsules: Alu. Alu. Blister Pack of 2 x 7's.
Axesom 40mg Capsules: Alu. Alu. Blister Pack of 2 x 7's.

ایکسم®
(ایسومیپرازول)

خوراک و ہدایات:
صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

Manufactured by
HIGHNOON LABORATORIES LTD
17.5 KM, Multan Road, Lahore, Pakistan.
www.highnoon-labs.com

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