210 mm

140 mm

Migxen Tablet 85/500mg

(Sumatriptan + Naproxen Sodium)

مگزین ۸۵/۵۰۰ ملی گرام

(سوماٹرپٹان + نیپروکسن سوڈیم)

WARNING: NSAIDs cause an increased risk of serious cardiovascular thrombotic events, gastrointestinal bleeding, ulcerations and perforations.

COMPOSITION

Each film coated tablet contains:

Sumatriptan as succinate……85mg

Naproxen sodium ……500mg

(Innovator's Specifications)

DESCRIPTION

Migxen tablet contains sumatriptan (as succinate), a selective 5-hydroxytryptamine1 (5-HT1) receptor subtype agonist, and naproxen sodium, a member of the arylacetic acid group of NSAIDs.

INDICATIONS

Migxen tablet is indicated for the acute treatment of migraine with or without aura in adults and pediatric patients 12 years of age and older.

Limitations of Use:

- Use only if a clear diagnosis of migraine headache has been established. If a patient has no response to the first migraine attack treated with MIGXEN, reconsider the diagnosis of migraine before MIGXEN is administered to treat any subsequent attacks.
- MIGXEN is not indicated for the prevention of migraine attacks.
- Safety and effectiveness of MIGXEN have not been established for cluster headache.

MECHANISM OF ACTION

MIGXEN contains sumatriptan and naproxen.

Sumatriptan binds with high affinity to cloned 5-HT1B/1D receptors. Sumatriptan presumably exerts its therapeutic effects in the treatment of migraine headache through agonist effects at the 5-HT1B/1D receptors on intracranial blood vessels and sensory nerves of the trigeminal system, which result in cranial vessel constriction and inhibition of neuropeptide release.

MIGXEN has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of MIGXEN, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

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 a decrease of prostaglandins in peripheral tissues.

DOSAGE & ADMINISTRATION

Dosage in Adults:

The recommended dosage for adults is one tablet of MIGXEN 85mg/500mg. MIGXEN 85mg/500mg contains a dose of Sumatriptan higher than the lowest effective dose. The choice of the dose of Sumatriptan, and of the use of a fixed combination such as in MIGXEN 85mg/500mg should be made on an individual basis, weighing the possible benefit of a higher dose of sumatriptan with the potential for a greater risk of adverse reactions.

The maximum recommended dosage in a 24-hour period is two tablets, taken at least 2 hours apart.

The safety of treating an average of more than five migraine headaches in adults in a 30-day period has not been established.

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

Dosage in Pediatric Patients 12 to 17 Years of Age

The recommended dosage for pediatric patients 12 to 17 years of age is one tablet of sumatriptan and naproxen sodium 10mg / 60mg.

The maximum recommended dosage in a 24-hour period is one tablet of MIGXEN 85/500 mg.

The safety of treating an average of more than two migraine headaches in pediatric patients in a 30-day period has not been established.

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

Dosing in Patients with Hepatic Impairment

MIGXEN is contraindicated in patients with severe hepatic impairment.

In patients with mild to moderate hepatic impairment, the recommended dosage in a 24-hour period is one tablet of MIGXEN

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

PHARMACOKINETICS

Absorption and Bioavailability

Sumatriptan, when given as MIGXEN 85 mg / 500 mg, has a mean C_{max} similar to that of sumatriptan succinate 100 mg tablets alone. The median T_{max} of sumatriptan, when given as MIGXEN 85 mg /500 mg, was 1 hour (range: 0.3 to 4.0 hours), which is slightly different compared with sumatriptan succinate 100 mg tablets (median T_{max} of 1.5 hours). Naproxen, when given as MIGXEN 85 mg /500 mg, has a C_{max} which is approximately 36% lower than naproxen sodium 550 mg tablets and a median T_{max} of 5 hours (range: 0.3 to 12 hours), which is approximately 4 hours later than from naproxen sodium tablets 550 mg. AUC values for sumatriptan and for naproxen are similar for MIGXEN 85 mg /500 mg compared with sumatriptan succinate 100 mg tablets or naproxen sodium 550 mg tablets, respectively. In a crossover trial in 16 subjects, the pharmacokinetics of both components administered as MIGXEN 85 mg /500 mg were similar during a migraine attack and during a migraine-free period.

Bioavailability of sumatriptan is approximately 15%, primarily due to presystemic (first-pass) metabolism and partly due to incomplete absorption.

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

Food had no significant effect on the bioavailability of sumatriptan or naproxen administered as MIGXEN, but slightly delayed the T_{max} of sumatriptan by about 0.6 hour.

Distribution

Plasma protein binding is 14% to 21%. The effect of sumatriptan on the protein binding of other drugs has not been evaluated. The volume of distribution of sumatriptan is 2.7 L/kg.

The volume of distribution of naproxen is 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 a 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-; 1,000-; and 1,500-mg daily doses of naproxen, respectively). However, the concentration of unbound naproxen continues to increase proportionally to dose.

Metabolism

In vitro studies with human microsomes suggest that sumatriptan is metabolized by monoamine oxidase (MAO), predominantly the A-isoenzyme. No significant effect was seen with an MAO-B inhibitor

Naproxen is extensively metabolized to 6-0-desmethyl naproxen, and both parent and metabolites do not induce metabolizing enzymes.

Elimination

The elimination half-life of sumatriptan is approximately 2 hours. Radiolabeled ^{14}C-sumatriptan administered orally is largely excreted renally (about 60%), with about 40% found in the feces. Most of a radiolabeled dose of sumatriptan excreted in the urine is the major metabolite indole acetic acid (IAA) or the IAA glucuronide, both of which are inactive. Three percent of the dose can be recovered as unchanged sumatriptan.

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 (less than 1%), 6-0-desmethyl naproxen (less than 1%), or their conjugates (66% to 70%). The plasma half-life of the naproxen anion in humans is approximately 19 hours. The corresponding half-lives of both metabolites and conjugates of naproxen are shorter than 12 hours, and their rates of excretion have been found to coincide closely with the rate of naproxen disappearance from the plasma. In patients with renal failure, metabolites may accumulate.

WARNINGS & PRECAUTIONS

Cardiovascular Thrombotic Events

The use of MIGXEN is contraindicated in patients with ischemic or vasospastic coronary artery disease (CAD) and in the setting of coronary artery bypass graft (CABG) surgery due to increased risk of serious cardiovascular events with sumatriptan and NSAIDS.

Cardiovascular Events with Sumatriptan

There have been rare reports of serious cardiac adverse reactions, including acute myocardial infarction, occurring within a few hours following administration of sumatriptan. Some of these reactions occurred in patients without known CAD. MIGXEN may cause coronary artery vasospasm (Prinzmetal's angina), even in patients without a history of CAD.

Cardiovascular Thrombotic Events with Nonsteroidal Anti-inflammatory Drugs

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as naproxen, increases the risk of serious gastrointestinal (GI) events.

Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG.

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of re-infarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Perform a cardiovascular evaluation in patients who have multiple cardiovascular risk factors (e.g., increased age, diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to receiving MIGXEN**.** If there is evidence of CAD or coronary artery vasospasm, MIGXEN is contraindicated. For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administering the first dose of MIGXEN in a medically supervised setting and performing an electrocardiogram (ECG) immediately following administration of MIGXEN**.** For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of MIGXEN.

Physicians and patients should remain alert for the development of cardiovascular events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of serious cardiovascular events and the steps to take if they occur.

Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including naproxen, a component of MIGXEN, cause serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only 1 in 5 patients who develop a serious upper gastrointestinal adverse event on NSAID therapy is symptomatic. Upper gastrointestinal ulcers, gross bleeding, or perforation caused by NSAIDs appear to occur in approximately 1% of patients treated daily for 3 to 6 months and in about 2% to 4% of patients treated for 1 year. However, even short-term therapy is not without risk.

Among 3,302 adult patients with migraine who received MIGXEN in controlled and uncontrolled clinical trials, 1 patient experienced a recurrence of gastric ulcer after taking 8 doses over 3 weeks, and 1 patient developed a gastric ulcer after treating an average of 8 attacks per month over 7 months.

Risk Factors for GI Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing gastrointestinal bleeding compared with patients with neither of these risk factors. Other factors that increase the risk for gastrointestinal bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most post-marketing reports of fatal gastrointestinal events occurred in elderly or debilitated patients, and therefore special care should be taken in treating this population. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For high risk patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue MIGXEN until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding.

Arrhythmias

Life-threatening disturbances of cardiac rhythm, including ventricular tachycardia and ventricular fibrillation leading to death, have been reported within a few hours following the administration of 5-HT1 agonists. Discontinue MIGXEN if these disturbances occur.

MIGXEN is contraindicated in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders.

Chest, Throat, Neck, and/or Jaw Pain/Tightness/Pressure

Sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck, and jaw commonly occur after treatment with sumatriptan and are usually non-cardiac in origin. However, perform a cardiac evaluation if these patients are at high cardiac risk. The use of MIGXEN is contraindicated in patients with CAD and those with Prinzmetal's variant angina.

Cerebrovascular Events

Cerebral hemorrhage, subarachnoid hemorrhage, and stroke have occurred in patients treated with 5-HT1 agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the 5-HT1 agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. Also, patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, TIA). Discontinue MIGXEN if a cerebrovascular event occurs. Before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, exclude other potentially serious neurological conditions. MIGXEN is contraindicated in patients with a history of stroke or TIA.

Other Vasospasm Reactions

Sumatriptan may cause non-coronary vasospastic reactions, such as peripheral vascular ischemia, gastrointestinal vascular ischemia and infarction (presenting with abdominal pain and bloody diarrhea), splenic infarction, and Raynaud's syndrome. In patients who experience symptoms or signs suggestive of non-coronary vasospasm reaction following the use of any 5-HT1 agonist, rule out a vasospastic reaction before receiving additional MIGXEN.

Reports of transient and permanent blindness and significant partial vision loss have been reported with the use of 5-HT1 agonists. Since visual disorders may be part of a migraine attack, a causal relationship between these events and the use of 5-HT1 agonists have not been clearly established.

Hepatotoxicity

Borderline elevations of 1 or more liver tests may occur in up to 15% of patients who take NSAIDs including naproxen, a component of MIGXEN**.** Hepatic abnormalities may be the result of hypersensitivity rather than direct toxicity. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Notable (3 times the upper limit of normal) elevations of SGPT (ALT) or SGOT (AST) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare, sometimes fatal cases of severe hepatic injury, including jaundice and fatal fulminant hepatitis, liver necrosis, and hepatic failure have been reported with NSAIDs.

MIGXEN is contraindicated in patients with severe hepatic impairment. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with MIGXEN. MIGXEN should be discontinued if clinical signs and symptoms consistent with liver disease develop, if systemic manifestations occur (e.g., eosinophilia, rash), or if abnormal liver tests persist or worsen. Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flulike" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue MIGXEN immediately, and perform a clinical evaluation of the patient.

Hypertension

Significant elevation in blood pressure, including hypertensive crisis with acute impairment of organ systems, has been reported on rare occasions in patients treated with 5-HT1 agonists, including sumatriptan, a component of MIGXEN. This occurrence has included patients without a history of hypertension.

NSAIDs, including naproxen, a component of MIGXEN, can also lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of cardiovascular events. Patients taking angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs.

Monitor blood pressure in patients treated with MIGXEN. MIGXEN is contraindicated in patients with uncontrolled hypertension.

Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death. Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of naproxen may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]). Avoid the use of MIGXEN in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If MIGXEN is used in patients with severe heart failure, monitor patients for signs of worsening heart failure. Since each MIGXEN 85/500 mg tablet contains approximately 60 mg of sodium and each MIGXEN 10/60 mg tablet contains approximately 20 mg of sodium, this should be considered in patients whose overall intake of sodium must be severely restricted.

Medication Overuse Headache

Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, or a combination of these drugs for 10 or more days per month) may lead to exacerbation of headache (medication overuse headache). Medication overuse headache may present as migraine-like daily headaches, or as a marked increase in frequency of migraine attacks. Detoxification of patients, including withdrawal of the overused drugs, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

210 mm

140 mm

Serotonin Syndrome

Serotonin syndrome may occur with MIGXEN, particularly during co-administration with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and MAO inhibitors. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms usually occurs within minutes to hours of receiving a new or a greater dose of a serotonergic medication. Discontinue MIGXEN if serotonin syndrome is suspected.

Renal Toxicity

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 an 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, dehydration, hypovolemia, heart failure, liver dysfunction, salt depletion, those taking diuretics and angiotensin-converting enzyme (ACE) inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.
MIGXEN should be discontinued if clinical signs and symptoms consistent with renal disease develop or if systemic manifestations occur.
MIGXEN is not recommended for use in patients with severe renal impairment (creatinine clearance [CrCl] <30 mL/min) unless the benefits are expected to outweigh the risk of worsening renal function. If MIGXEN is used in patients with advanced renal disease, monitor patients for signs of worsening renal function. Monitor renal function in patients with mild (CrCl = 60 to 89 mL/min) or moderate (CrCl = 30 to 59 mL/min) renal impairment, preexisting kidney disease, or dehydration.
The renal effects of MIGXEN may hasten the progression of renal dysfunction in patients with pre-existing renal disease.
Correct volume status in dehydrated or hypovolemic patients prior to initiating MIGXEN. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of MIGXEN. Avoid the use of MIGXEN in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If MIGXEN is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with the use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronsim state.

Anaphylactic Reactions

Anaphylactic reactions may occur in patients without known prior exposure to either component of MIGXEN. Such reactions can be life-threatening or fatal. In general, anaphylactic reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens although anaphylactic reactions with naproxen have occurred in patient without known hypersensitivity to naproxen or to patients with aspirin sensitive asthma. MIGXEN should not be given to patients with the aspirin triad. This symptom complex typically occurs in patients with asthma who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs.
MIGXEN is contraindicated in patients with a history of hypersensitivity reaction to sumatriptan, naproxen, or any other component of MIGXEN**.** Naproxen has been associated with anaphylactic reactions in patients without known hypersensitivity to naproxen and in patients with aspirin-sensitive asthma. Seek emergency help if an anaphylactic reaction occurs.

Serious Skin Reactions

NSAID-containing products can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions and to discontinue the use of MIGXEN at the first appearance of skin rash or any other sign of hypersensitivity. MIGXEN is contraindicated in patients with previous serious skin reactions to NSAIDs.

Premature Closure of the Ductus Arteriosus

MIGXEN may cause premature closure of the ductus arteriosus. Avoid use of NSAIDs, including MIGXEN, in pregnant women starting at 30 weeks of gestation (third trimester).

Hematologic Toxicity

Anemia has occurred in patients receiving NSAIDs. This may be due to fluid retention, occult or gross gastrointestinal blood loss, or an incompletely described effect upon erythropoiesis. If a patient treated with MIGXEN has signs or symptoms of anemia, monitor hemoglobin or hematocrit.
NSAIDs, including MIGXEN, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding.

Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, MIGXEN is contraindicated in patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma. When MIGXEN is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

Seizures

Seizures have been reported following administration of sumatriptan. Some have occurred in patients with either a history of seizures or concurrent conditions predisposing to seizures. There are also reports in patients where no such predisposing factors are apparent. MIGXEN should be used with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold.

Masking of Inflammation and Fever

The pharmacological activity of MIGXEN in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

Laboratory Monitoring

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically.

Pregnancy

Pregnancy Category C during the first two trimesters of pregnancy; Category X during the third trimester of pregnancy. There are no adequate and well-controlled studies in pregnant women. MIGXEN (sumatriptan and naproxen) should be used during the first and second trimester of pregnancy only if the potential beneft justifies the potential risk to the fetus. MIGXEN should not be used during the third trimester of pregnancy because inhibitors of prostaglandin synthesis (including naproxen) are known to cause premature closure of the ductus arteriosus in humans. In animal studies, administration of sumatriptan and naproxen, alone or in combination, during pregnancy resulted in developmental toxicity (increased incidences of fetal malformations, embryofetal and pup mortality, decreased embryofetal growth) at clinically relevant doses.

Labor and Delivery

Naproxen-containing products are not recommended in labor and delivery because, through its prostaglandin synthesis inhibitory effect, naproxen may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage. In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred.

Nursing Mothers

Both active components of MIGXEN, sumatriptan and naproxen, have been reported to be secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from MIGXEN, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

SIDE EFFECTS

The following serious side effects are described below and elsewhere in labeling:

- Cardiovascular Thrombotic Events
- GI Bleeding, Ulceration and Perforation
- Arrhythmias
- Chest, Throat, Neck, and/or Jaw Pain/Tightness/Pressure
- Cerebrovascular Events & Other Vasospasm Reactions
- Hepatotoxicity
- Hypertension
- Heart Failure and Edema
- Medication Overuse Headache
- Serotonin Syndrome
- Renal Toxicity and Hyperkalemia
- Anaphylactic Reactions
- Serious Skin Reactions
- Hematological Toxicity
- Exacerbation Asthma Related to Aspirin Sensitivity
- Seizures

DRUG INTERACTIONS

Ergot-Containing Drugs

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions.
Because these effects may be additive, coadministration of MIGXEN and ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) within 24 hours of each other is contraindicated.

Monoamine Oxidase-A Inhibitors

MAO-A inhibitors increase systemic exposure of orally administered sumatriptan by 7-fold.
The use of MIGXEN in patients receiving MAO-A inhibitors is contraindicated.

Other 5-HT1 Agonists

5-HT1 agonist drugs can cause vasospastic effects.
Because these effects may be additive, coadministration of MIGXEN and other 5 HT1 agonists (e.g., triptans) within 24 hours of each other is contraindicated.

Drugs That Interfere with Hemostasis

Naproxen and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of naproxen and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
Monitor patients with concomitant use of MIGXEN with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding.

Aspirin

Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone.
Concomitant use of MIGXEN and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding.

Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome.

Cases of serotonin syndrome have been reported during co-administration of triptans and SSRIs, SNRIs, TCAs, and MAO inhibitors
Discontinue MIGXEN if serotonin syndrome is suspected.

ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-blockers

NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol).
In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
During concomitant use of MIGXEN and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained.
During concomitant use of MIGXEN and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function.

Diuretics

Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.
During concomitant use of MIGXEN with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects.

Digoxin

The concomitant use of naproxen with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
During concomitant use of MIGXEN and digoxin, monitor serum digoxin levels.

Lithium

NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
During concomitant use of MIGXEN and lithium, monitor patients for signs of lithium toxicity.

Methotrexate

Concomitant administration of some NSAIDs with high-dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity. Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
During concomitant use of MIGXEN and methotrexate, monitor patients for methotrexate toxicity.

Cyclosporine

Concomitant use of NSAIDs and cyclosporine may increase cyclosporine's nephrotoxicity.
During concomitant use of MIGXEN and cyclosporine, monitor patients for signs of worsening renal function.

NSAIDs and Salicylates

Concomitant use of naproxen with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy.
The concomitant use of naproxen with other NSAIDs or salicylates is not recommended.

Pemetrexed

Concomitant use of NSAIDs and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity

During concomitant use of MIGXEN and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.

Probenecid

Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly. The clinical significance of this is unknown.
Reduce the frequency of administration of Migxen when given concurrently with probenecid.

Drug/Laboratory Test Interactions

Blood Tests

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

Urine Tests

The administration of naproxen sodium 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 artificially 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).

CONTRAINDICATIONS

MIGXEN is contraindicated in the following patients:

- Ischemic coronary artery disease (CAD) (angina pectoris, history of myocardial infarction, or documented silent ischemia) or coronary artery vasospasm, including Prinzmetal's angina.
- In the setting of coronary artery bypass graft (CABG) surgery.
- Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders.
- History of stroke or transient ischemic attack (TIA) or history of hemiplegic or basilar migraine because these patients are at a higher risk of stroke.
- Peripheral vascular disease.
- Ischemic bowel disease.
- Uncontrolled hypertension.
- Recent use (i.e., within 24 hours) of ergotamine-containing medication, ergot-type medication (such as dihydroergotamine or methysergide), or another 5-hydroxytryptamine1 (5-HT1) agonist.
- Concurrent administration of a monoamine oxidase (MAO)-A inhibitor or recent (within 2 weeks) use of an MAO-A inhibitor
- History of asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients.
- Known hypersensitivity (e.g., anaphylactic reactions, angioedema, and serious skin reactions) to sumatriptan, naproxen, or any components of MIGXEN.
- Third trimester of pregnancy.
- Severe hepatic impairment.

OVERDOSE

Overdose of sumatriptan in animals has been fatal and has been heralded by convulsions, tremor, paralysis, inactivity, ptosis, erythema of the extremities, abnormal respiration, cyanosis, ataxia, mydriasis, salivation, and lacrimation.
Symptoms following acute NSAID over dosages have been typically limited to lethargy, drowsiness, nausea, vomiting and epigastric pain. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare .
Manage patients with symptomatic and supportive care following an NSAID over dosage. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large over dosage (5 to 10 times the recommended dosage). Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of sumatriptan. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

STORAGE & INSTRUCTIONS

Store between 15-30ºC.
Protect from heat, sunlight and moisture.
Keep away from the reach of the children.
To be sold on the prescription of a registered medical practitioner only.

HOW SUPPLIED

Migxen tablet 85mg / 500mg
2's, 6's, 10's Tablets

غرائک طریقہ استعمال:

ڈاکٹری ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو دھوپ، ۳۰ ڈگری سینٹی گریڈ سے زیادہ حرارت کے دوران نہ رکھیں۔
دھوپ، گرمی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

HOW SUPPLIED

Migxen tablet 85mg / 500mg

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

Manufactured by:

PHARMASOL PRIVATE LIMITED

Plot # 549,Sundar Industrial Estate,
Lahore, Pakistan.