AnexM®

(Sumatriptan + Naproxen Sodium)

انیکس-ایم

COMPOSITION
Each film coated tablet contains:
Sumatriptan Succinate BP 119mg eq. to
Sumatriptan (as free base) 85mg
Naproxen Sodium USP 500mg
(As per Innovator's Specs.)

BLACK BOX WARNING

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

• Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.

• Sumatriptan + Naproxen combination is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.

• NSAIDs cause an increased risk of serious gastrointestinal (GI) 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 and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.

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

CLINICAL PHARMACOLOGY

Mechanism of Action
ANEX-M 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.

ANEX-M has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of ANEX-M, 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.

Pharmacodynamics
In a healthy volunteer study, 10 days of concomitant administration of naproxen 220 mg once-daily with low-dose immediate-release aspirin (81 mg) showed an interaction with the antiplatelet activity of aspirin as measured by % serum thromboxane B2 inhibition at 24 hours following the day 10 dose [98.7% (aspirin alone) vs 93.1% (naproxen and aspirin)]. The interaction was observed even following discontinuation of naproxen on day 11 (while aspirin dose was continued) but normalized by day 13. In the same study, the interaction was greater when naproxen was administered 30 minutes prior to aspirin [98.7% vs 87.7%] and minimal when aspirin was administered 30 minutes prior to naproxen [98.7% vs 95.4%].

Following administration of naproxen 220 mg twice-daily with low-dose immediate–release aspirin (first naproxen dose given 30 minutes prior to aspirin), the interaction was minimal at 24 h following day 10 dose [98.7% vs 95.7%]. However, the interaction was more prominent after discontinuation of naproxen (washout) on day 11 [98.7% vs 84.3%] and did not normalize completely by day 13 [98.5% vs 90.7%].

Blood Pressure
In a randomized, double-blind, parallel group, active control trial, Sumatriptan/ Naproxen combination 85/500 mg administered intermittently over 6 months did not increase blood pressure in a normotensive adult population (n = 122). However, significant elevation in blood pressure has been reported with 5-HT1 agonists and NSAIDs in patients with and without a history of hypertension.

Pharmacokinetics
Absorption
Sumatriptan, when given as Sumatriptan/ Naproxen combination 85/500 mg, has a mean Cmax similar to that of sumatriptan succinate 100 mg tablets alone. The median Tmax of sumatriptan, when given as Sumatriptan/ Naproxen combination 85/500 mg, was 1 hour (range: 0.3 to 4.0 hours), which is slightly different compared with sumatriptan succinate 100 mg tablets (median Tmax of 1.5 hours). Naproxen, when given as Sumatriptan/ Naproxen combination 85/500 mg, has a Cmax which is approximately 36% lower than naproxen sodium 550 mg tablets and a median Tmax 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 Sumatriptan/ Naproxen combination 85/500 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 Sumatriptan/ Naproxen combination 85/500 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 Sumatriptan/ Naproxen combination, but slightly delayed the Tmax 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 14C-sumatriptan administered orally is largely renally excreted (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 92%). 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.

Pharmacokinetics in special populations
Geriatrics

The pharmacokinetics of Sumatriptan/ Naproxen combination in geriatric patients have not been studied. Elderly patients are more likely to have decreased hepatic function and decreased renal function.

The pharmacokinetics of oral sumatriptan in the elderly (mean age: 72 years, 2 males and 4 females) and in patients with migraine (mean age: 38 years, 25 males and 155 females) were similar to that in healthy male subjects (mean age: 30 years).

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction, which represents <1% of the total concentration, increased in the elderly (range of unbound trough naproxen from 0.12% to 0.19% in elderly subjects versus 0.05% to 0.075% in younger subjects).

Pediatrics
A pharmacokinetic study compared 3 doses of Sumatriptan/ Naproxen combination in pediatric patients 12 to 17 years of age (n=24) with adults (n=26). The AUC and Cmax of sumatriptan were 50-60% higher following a single dose of Sumatriptan/ Naproxen combination 10/60 mg in pediatric patients 12 to 17 years of age (n=7) compared with adult subjects (n=8), and were 6-26% higher following a single dose of Sumatriptan/ Naproxen combination 30/180 mg or 85/500 mg in pediatrics than adults. Naproxen pharmacokinetic parameters were similar between pediatrics and adults.

Renal Impairment
The effect of renal impairment on the pharmacokinetics of Sumatriptan/ Naproxen combination has not been studied. Since naproxen and 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.

Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of Sumatriptan/ Naproxen combination has not been studied. In a study in patients with moderate hepatic impairment (n = 8) matched for sex, age, and weight with healthy subjects (n = 8), patients with hepatic impairment had an approximately 70% increase in AUC and Cmax of sumatriptan and a Tmax 40 minutes earlier compared to healthy subjects. The pharmacokinetics of sumatriptan in patients with severe hepatic impairment has not been studied.

INDICATIONS
ANEX-M 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 ANEX-M, reconsider the diagnosis of migraine before ANEX-M is administered to treat any subsequent attacks.
• ANEX-M is not indicated for the prevention of migraine attacks.
• Safety and effectiveness of ANEX-M have not been established for cluster headache.

DOSAGE AND ADMINISTRATION
Dosage in Adults
The recommended dosage for adults is 1 tablet of ANEX-M 85/500 mg. ANEX-M 85/500 mg 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 ANEX-M 85/500 mg 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 2 tablets, taken at least 2 hours apart.

The safety of treating an average of more than 5 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 1 tablet of ANEX-M 10/60 mg.

The maximum recommended dosage in a 24-hour period is 1 tablet of ANEX-M 85/500 mg.
The safety of treating an average of more than 2 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.

CONTRAINDICATIONS
ANEX-M 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).
• 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 faal, 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 ANEX-M.
• Severe hepatic impairment

WARNING AND PRECAUTIONS
Cardiovascular Thrombotic Events
The use of ANEX-M 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. ANEX-M 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.

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 reinfarction, 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 ANEX-M. If there is evidence of CAD or coronary artery vasospasm, ANEX-M is contraindicated. For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administering the first dose of ANEX-M in a medically supervised setting and performing an electrocardiogram (ECG) immediately following administration of ANEX-M. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of ANEX-M.

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 ANEX-M, 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.

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 postmarketing 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 ANEX-M 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 ANEX-M if these disturbances occur.

ANEX-M 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 ANEX-M 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 ANEX-M 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. ANEX-M 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 ANEX-M.

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 ANEX-M. 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.

ANEX-M 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 ANEX-M. ANEX-M 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 ANEX-M 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 ANEX-M. This occurrence has included patients without a history of hypertension.

NSAIDs, including naproxen, a component of ANEX-M, 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 ANEX-M. ANEX-M 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 ANEX-M in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If ANEX-M is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

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.

Serotonin Syndrome
Serotonin syndrome may occur with ANEX-M, particularly during coadministration 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 ANEX-M if serotonin syndrome is suspected.

Renal Toxicity and Hyperkalemia

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.

ANEX-M should be discontinued if clinical signs and symptoms consistent with renal disease develop or if systemic manifestations occur.

ANEX-M 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 ANEX-M 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 ANEX-M 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 ANEX-M. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of ANEX-M. Avoid the use of ANEX-M in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If ANEX-M 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-hypoaldosteronism state.

Anaphylactic Reactions

Anaphylactic reactions may occur in patients without known prior exposure to either component of ANEX-M. 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. ANEX-M 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.

ANEX-M is contraindicated in patients with a history of hypersensitivity reaction to sumatriptan, naproxen, or any other component of ANEX-M. 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 ANEX-M at the first appearance of skin rash or any other sign of hypersensitivity. ANEX-M is contraindicated in patients with previous serious skin reactions to NSAIDs.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as ANEX-M. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue ANEX-M and evaluate the patient immediately.

Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus: Avoid use of NSAIDs, including ANEX-M, in pregnant women at about 30 weeks gestation and later. NSAIDs, including ANEX-M, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment: Use of NSAIDs, including ANEX-M, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit ANEX-M use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if ANEX-M treatment extends beyond 48 hours. Discontinue ANEX-M if oligohydramnios occurs and follow up according to clinical practice.

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 ANEX-M has signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including ANEX-M, 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, ANEX-M is contraindicated in patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

When ANEX-M 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. ANEX-M 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 ANEX-M 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.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults

The adverse reactions reported below are specific to the clinical trials with Sumatriptan/ Naproxen combination 85/500 mg.

Table 1 lists adverse reactions that occurred in 2 placebo-controlled clinical trials (Study 1 and 2) in adult patients who received 1 dose of study drug. Only adverse reactions that occurred at a frequency of 2% or more in any group treated with Sumatriptan/

Table 1. Adverse Reactions in Pooled Placebo-Controlled Trials in Adult Patients with Migraine

Adverse Reactions	Sumatriptan / Naproxen combination 85/500 mg % (n = 737)	Placebo % (n = 752)	Sumatriptan 85 mg % (n = 735)	Naproxen Sodium 500 mg % (n = 732)
Nervous system disorders				
Dizziness	4	2	2	2
Somnolence	3	2	2	2
Paresthesia	2	<1	2	<1
Gastrointestinal disorders				
Nausea	3	1	3	<1
Dyspepsia	2	1	2	1
Dry mouth	2	1	2	<1
Pain and other pressure sensations				
Chest discomfort/chest pain	3	<1	2	1
Neck/throat/jaw pain/tightness/pressure	3	1	3	1

Naproxen combination 85/500 mg and that occurred at a frequency greater than the placebo group are included in Table 1.
The incidence of adverse reactions in controlled clinical trials was not affected by gender or age of the patients. There were insufficient data to assess the impact of race on the incidence of adverse reactions.

Pediatric Patients 12 to 17 Years of Age In a placebo-controlled clinical trial that evaluated pediatric patients 12 to 17 years of age who received 1 dose of Sumatriptan/ Naproxen combination 10/60 mg, 30/180 mg, or 85/500 mg, adverse reactions occurred in 13% of patients who received 10/60 mg, 9% of patients who received 30/180 mg, 13% who received 85/500 mg, and 8% who received placebo. No patients who received Sumatriptan/ Naproxen combination experienced adverse reactions leading to withdrawal from the trial. The incidence of adverse reactions in pediatric patients 12 to 17 years of age was comparable across all 3 doses compared with placebo. Table 2 lists adverse reactions that occurred in a placebo-controlled trial in pediatric patients 12 to 17 years of age at a frequency of 2% or more with Sumatriptan/ Naproxen combination and were more frequent than the placebo group.

Adverse Reactions	Sumatriptan/ Naproxen combination 10/60 mg % (n = 96)	Sumatriptan/ Naproxen combination 30/180 mg % (n = 97)	Sumatriptan/ Naproxen combination 85/500 mg % (n = 152)	Placebo % (n = 145)
Vascular Hot flush (i.e., hot flash[es])	0	2	<1	0
Musculoskeletal Muscle tightness	0	0	2	0

DRUG INTERACTIONS

Clinically Significant Drug Interactions with Naproxen or Sumatriptan

Ergot-Containing Drugs	
Clinical Impact:	Ergot-containing drugs have been reported to cause prolonged vasospastic reactions.
Intervention:	Because these effects may be additive, coadministration of ANEX-M and ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) within 24 hours of each other is contraindicated.
Monoamine Oxidase-A Inhibitors	
Clinical Impact:	MAO-A inhibitors increase systemic exposure of orally administered sumatriptan by 7-fold.
Intervention:	The use of ANEX-M in patients receiving MAO-A inhibitors is contraindicated.
Other 5-HT1 Agonists	
Clinical Impact:	5-HT1 agonist drugs can cause vasospastic effects.
Intervention:	Because these effects may be additive, coadministration of ANEX-M and other 5 HT1 agonists (e.g., triptans) within 24 hours of each other is contraindicated.
Drugs That Interfere with Hemostasis	
Clinical Impact:	• 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.
Intervention:	Monitor patients with concomitant use of ANEX-M 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	
Clinical Impact:	A pharmacodynamic (PD) study has demonstrated an interaction in which lower dose naproxen (220mg/day or 220mg twice daily) interfered with the antiplatelet effect of low-dose immediate-release aspirin, with the interaction most marked during the washout period of naproxen. There is reason to expect that the interaction would be present with prescription doses of naproxen or with enteric-coated low-dose aspirin; however, the peak interference with aspirin function may be later than observed in the PD study due to the longer washout period. 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.
Intervention:	Because there may be an increased risk of cardiovascular events following discontinuation of naproxen due to the interference with the antiplatelet effect of aspirin during the washout period, for patients taking low-dose aspirin for cardioprotection who require intermittent analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of aspirin, or non-NSAID analgesics where appropriate. Concomitant use of ANEX-M 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	
Clinical Impact:	Cases of serotonin syndrome have been reported during coadministration of triptans and SSRIs, SNRIs, TCAs, and MAO inhibitors.
Intervention:	Discontinue ANEX-M if serotonin syndrome is suspected.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-blockers	
Clinical Impact:	• 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.
Intervention:	• During concomitant use of ANEX-M and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of ANEX-M 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 Impact:	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.
Intervention:	During concomitant use of ANEX-M with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects.
Digoxin	
Clinical Impact:	The concomitant use of naproxen with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention:	During concomitant use of ANEX-M and digoxin, monitor serum digoxin levels.
Lithium	
Clinical Impact:	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.
Intervention:	During concomitant use of ANEX-M and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	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).
Intervention:	During concomitant use of ANEX-M and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of NSAIDs and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of ANEX-M and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
Clinical Impact:	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
Intervention:	The concomitant use of naproxen with other NSAIDs or salicylates is not recommended.
Probenecid	
Clinical Impact:	Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly. The clinical significance of this is unknown.
Intervention:	Reduce the frequency of administration of ANEX-M when given concurrently with probenecid.

USE IN SPECIAL POPULATIONS

• Pregnancy

Use of NSAIDs, including ANEX-M, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of ANEX-M use between about 20 and 30 weeks of gestation, and avoid ANEX-M use at about 30 weeks of gestation and later in pregnancy.

• Nursing mother

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. Sumatriptan is excreted in human milk following subcutaneous administration. There is no information regarding sumatriptan concentrations in milk from lactating women following administration of sumatriptan tablets.

There are no data on the effects of naproxen or sumatriptan on the breastfed infant or the effects of naproxen or sumatriptan on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ANEX-M and any potential adverse effects on the breastfed infant from ANEX-M or from the underlying maternal condition.

• Pediatrics

Safety and effectiveness of ANEX-M in pediatric patients under 12 years of age have not been established.

The safety and efficacy of ANEX-M for the acute treatment of migraine in pediatric patients 12 to 17 years of age was established in a double-blind, placebo-controlled trial.

• Elderly

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. ANEX-M is not recommended for use in elderly patients who have decreased renal function, higher risk for unrecognized CAD, and increases in blood pressure that may be more pronounced in the elderly.

A cardiovascular evaluation is recommended for geriatric patients who have other cardiovascular risk factors (e.g., diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to receiving ANEX-M.

• Renal impairment

ANEX-M is not recommended for use in patients with creatinine clearance less than 30 mL/min. Monitor the serum creatinine or creatinine clearance 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.

• Hepatic impairment

ANEX-M is contraindicated in patients with severe hepatic impairment. For patients with mild or moderate hepatic impairment, the ANEX-M dose should be reduced.

OVER DOSAGE

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 overdosages 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 overdosage. 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 overdosage (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.

PRESENTATION

ANEX-M 85/500mg : Pack of 2 tablets.

INSTRUCTIONS

Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture. Store below 30°C.
For suspected adverse drug reaction, email us at reports@pharmevo.biz

For more information on our products call PharmAssist helpline 0800-82222
Monday to Friday 9:00 am to 6:00 pm or email us at : pharmassist@pharmevo.biz

ہدایات:
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
تمام ادویات بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر ہی فروخت کی جائے۔
روشنی، گرمی اور نمی سے محفوظ رکھیں 30°C سے کم درجہ حرارت پر رکھیں۔
دوا کے ممکنہ مضر اثرات کے متعلق reports@pharmevo.biz پر مطلع کریں۔

ہماری ادویات کی مزید معلومات کے لئے فارماسسٹ کی ہیلپ لائن نمبر 0800-82222 پر کال کریں۔
یا پیر تا ہفتہ 9:00 بجے تا شام 6:00 بجے
یا ہمیں pharmassist@pharmevo.biz پر ای میل کریں

Manufactured by:
PharmEvo (Pvt.) Ltd.
Plot No. A-29, North Western Industrial Zone. Port Qasim, Karachi-75020, Pakistan.
www.pharmevo.biz

PharmEvo® Our dream, a healthier society

Rev: DI/ANEM/0010/002
120000742