For the use of Registered Medical Practitioner Only

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic 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
Naproprym-S is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal Bleeding, Ulceration, and Perforation
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.

1. **Generic Name and Brand Name**
   Sumatriptan and Naproxen Tablets
   Naproprym™-S

2. **Qualitative and Quantitative composition**
   Each film coated tablet contains:
   Sumatriptan I.P. ….. 85mg
   Naproxen I.P. ….. 500mg
   Excipients ….. q.s.
   Colours: Lake of Quinoline Yellow & Titanium Dioxide I.P.

3. **Dosage form and strength**
   Refer section 1 & 2

4. **Clinical Particulars**
   4.1. Therapeutic Indication
   For the treatment of acute migraine.

   4.2. Posology and Method of Administration
   Sumatriptan and Naproxen is a fixed combination containing doses of Sumatriptan (85mg) and Naproxen (500mg) within the approved dosage ranges of the individual components (25 to 100 mg of Sumatriptan and 220 to 825 mg of Naproxen). Sumatriptan and Naproxen contains a dose of Sumatriptan higher than the lowest effective dose. Individuals may vary in response to doses of Sumatriptan. The recommended dose is 1 tablet. The efficacy of taking a second dose has not been established. Do not take more than 2 Sumatriptan and Naproxen tablets in 24 hours. Dosing of tablets should be at least 2 hours apart.

Sumatriptan and Naproxen may be administered with or without food. Tablets should not be split, crushed, or chewed.

SPECIAL POPULATIONS
Renal Impairment: Sumatriptan and Naproxen is not recommended for use in patients with creatinine clearance less than 30 mL/min. The effect of renal impairment on the pharmacokinetics of Sumatriptan and Naproxen has not been studied. Minimal change in clinical effect would be expected with regard to Sumatriptan as it is largely metabolized to an inactive substance. 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: Because Sumatriptan and Naproxen is a fixed-dose combination that cannot be adjusted for this patient population, it is contraindicated in patients with hepatic impairment. The effect of hepatic impairment on the pharmacokinetics of Sumatriptan and Naproxen has not been studied. Sumatriptan is contraindicated in patients with severe hepatic impairment and the dose is limited to 50 mg in patients with liver disease.

Age: The effect of age (elderly or pediatric patients) on the pharmacokinetics of Sumatriptan and Naproxen has not been studied. Elderly patients are more likely to have decreased hepatic function and decreased renal function.

Gender: There is no effect of gender on the systemic exposure of Sumatriptan and Naproxen. In a study comparing the pharmacokinetics of Sumatriptan in females and males, no differences were observed between genders for AUC, Cmax, Tmax, and T½.

Race: The effect of race on the pharmacokinetics of Sumatriptan and Naproxen has not been studied. The systemic clearance and Cmax of Sumatriptan were similar in black (n = 34) and Caucasian (n = 38) healthy male subjects.

4.3. Contraindications

Cardiac, Cerebrovascular, or Peripheral Vascular Disease:
Sumatriptan and Naproxen should not be given to patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes. In addition, patients with other significant underlying cardiovascular diseases should not receive Sumatriptan and Naproxen, nor should patients who have had coronary artery bypass graft (CABG) surgery. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina, such as the Prinzmetal variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks. Peripheral vascular disease includes, but is not limited to, ischemic bowel disease

Uncontrolled Hypertension:

Sumatriptan and Naproxen should not be given to patients with uncontrolled hypertension because the components have been shown to increase blood pressure.

Monoamine Oxidase-A Inhibitors:
Concurrent administration of MAO-A inhibitors or use of Sumatriptan and Naproxen within 2 weeks of discontinuation of MAO-A inhibitor therapy is contraindicated

Ergotamine-Containing or Ergot-Type Medications:
Sumatriptan and Naproxen and any ergotamine-containing or ergot-type medication (like dihydroergotamine or methysergide) should not be used within 24 hours of each other.

Pregnancy:
Naproxen is contraindicated in the last trimester of pregnancy (after 28 weeks of pregnancy).

4.4. Special Warnings and precautions for use

Sumatriptan and Naproxen should only be used where a clear diagnosis of migraine headache has been established.

Cardiovascular Effects: Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events:
Sumatriptan and Naproxen should not be given to patients with documented ischemic or vasospastic coronary artery disease (CAD) or to patients with a history of CABG surgery. It is strongly recommended that Sumatriptan-containing products not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of CAD and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, Sumatriptan and Naproxen should not be administered. There are case reports associating Sumatriptan use with Takotsubo cardiomyopathy.

Risk of Gastrointestinal Ulceration, Bleeding, and Perforation with Nonsteroidal Anti-inflammatory Drug Therapy:
Sumatriptan and Naproxen contains an NSAID. NSAID-containing products can 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. These trends continue with longer duration of use, increasing the likelihood of developing a serious gastrointestinal event at some time during the course of therapy. However, even short-term therapy is not without risk. NSAID-containing products, should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. 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 to patients with neither of these risk factors. Other factors that increase the risk for gastrointestinal bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal gastrointestinal events are in elderly or debilitated patients, and therefore special care should be taken in treating this population. To minimize the potential risk for an adverse gastrointestinal event in patients treated with an NSAID-containing product, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of gastrointestinal ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious gastrointestinal adverse event is suspected. This should include discontinuation of the NSAID until a serious gastrointestinal adverse event is ruled out. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

Naproxen-Containing Products:
Sumatriptan and Naproxen and other Naproxen-containing products should not be used concomitantly since they all circulate in the plasma as the Naproxen anion.

Chest, Jaw, or Neck Pain/Discomfort:
Chest discomfort and jaw or neck tightness has been reported following use of Sumatriptan. Only rarely have these symptoms been associated with ischemic ECG changes.

Diseases That May Alter the Absorption, Metabolism, or Excretion of Drugs:
Sumatriptan and Naproxen should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as impaired renal function.

Seizures:
Sumatriptan and Naproxen should be used with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold. There have been reports of seizure following administration of Sumatriptan.

Hepatic Effects:
Sumatriptan and Naproxen is contraindicated in patients with 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 Sumatriptan and Naproxen. Borderline

elevations of 1 or more liver tests may occur in up to 15% of patients who take NSAID-containing products. 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, cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis, and hepatic failure, some of them with fatal outcomes, have been reported with NSAIDs.

4.5. Drugs interactions

Monoamine Oxidase-A Inhibitors: The use of Sumatriptan and Naproxen in patients receiving MAO-A inhibitors is contraindicated. MAO-A inhibitors reduce Sumatriptan clearance, significantly increasing systemic exposure. In patients taking MAO-A inhibitors, Sumatriptan plasma levels attained after treatment with recommended doses are 7-fold higher following oral administration than those obtained under other conditions.

Ergot-Containing Drugs: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (e.g., dihydroergotamine, methysergide) and Sumatriptan and Naproxen within 24 hours of each other should be avoided.

Methotrexate: Caution should be used if Sumatriptan and Naproxen is administered concomitantly with methotrexate. Naproxen and other NSAIDs have been reported to reduce the tubular secretion of methotrexate in an animal model, possibly increasing the toxicity of 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.

Aspirin: When Naproxen is administered with aspirin, its protein binding is reduced, although the clearance of free Naproxen is not altered. The clinical significance of this interaction is not known; however, as with other NSAID-containing products, concomitant administration of Sumatriptan and Naproxen and aspirin is not generally recommended because of the potential of increased adverse effects.

Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake:
Inhibitors and Serotonin Syndrome: Cases of life-threatening serotonin syndrome have been reported during combined use of SSRIs or SNRIs and triptans

Angiotensin-Converting Enzyme Inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors. The use of Sumatriptan and Naproxen in patients who are receiving ACE inhibitors may potentiate renal disease states

Furosemide: Clinical studies, as well as postmarketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During

concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure, as well as to assure diuretic efficacy.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when Sumatriptan and Naproxen and lithium are administered concurrently, patients should be observed carefully for signs of lithium toxicity.

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

Propranolol and Other Beta-Blockers: Propranolol 80 mg given twice daily had no significant effect on Sumatriptan pharmacokinetics. Naproxen and other NSAIDs can reduce the antihypertensive effect of propranolol and other beta-blockers.

Warfarin: The effects of warfarin and NSAIDs on gastrointestinal bleeding are synergistic, such that patients taking both drugs have a higher risk of serious gastrointestinal bleeding than patients taking either drug alone.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

PREGNANCY AND LACTATION

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. Sumatriptan and Naproxen should not be used in late pregnancy because NSAID-containing products have been shown to cause premature closure of the ductus arteriosus. Sumatriptan and Naproxen should not be used during early pregnancy unless the potential benefit justifies the potential risk to the fetus. Use of NSAIDs in pregnancy from week 20 and beyond may be associated with an increased risk of oligohydramnios (low levels of amniotic fluid surrounding the baby) and can lead to fetal renal dysfunction. Some cases of constriction of the ductus arteriosus (narrowing of a connecting blood vessel in the baby's heart) have also been identified at this early stage.

Lactation

Both active components of Sumatriptan and Naproxen, Sumatriptan and Naproxen, have been reported to be excreted in human breast milk. Because of the possible adverse effects of these drugs on neonates, use of Sumatriptan and Naproxen in nursing mothers should be avoided

Pediatric Use

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

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

Geriatric Use
Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. Naproprym-S 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.

4.7. Effects on ability to drive and use machines

Naproprym-S can cause dizziness, weakness, or drowsiness. If you have these symptoms, do not drive a car, use machinery, or do anything where you need to be alert.

4.8. Undesirable effects

Summary of safety profile

Since Naproprym-S contains both Sumatriptan succinate and Naproxen sodium, the same pattern of adverse reactions reported for these individual components may occur with the combination product.

Serious cardiac events, including some that have been fatal, have occurred following the use of 5-HT1 agonists, such as Sumatriptan. These events are very rare and most have been reported in patients with risk factors predictive of coronary artery disease (CAD). Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation.

The most common adverse reactions encountered with NSAIDs, such as Naproxen, are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred particularly in the elderly.

Most commonly reported adverse reactions in adults with Sumatriptan/Naproxen in clinical trials (incidence ≥2%) were: dizziness, somnolence, paresthesia, nausea, dry mouth, dyspepsia, chest discomfort. No new safety findings were identified during Sumatriptan/Naproxen treatment compared to the established safety profile for the individual substances.

Tabulated list of adverse reactions
Frequencies have been defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000); not known (cannot be estimated from the available data).

Sumatriptan

Organ System	**Common**	**Very rare**	**Not known**
Immune system disorders	-	-	Hypersensitivity reactions ranging

			from cutaneous hypersensitivity (such as urticaria) to anaphylaxis
Psychiatric disorders	-	-	Anxiety
Nervous system disorders	Dizziness, tingling, drowsiness, sensory disturbance including paraesthesia and hypoaesthesia	-	Seizures*, tremor, dystonia, nystagmus, scotoma
Eye disorders	-	-	Flickering, diplopia, reduced vision. Loss of vision including permanent defects**
Cardiac disorders	-	-	Bradycardia, tachycardia, palpitations, cardiac arrhythmias, transient ischaemic ECG changes, coronary artery vasospasm, angina, myocardial infarction (see sections 4.3 and 4.4)
Vascular disorders	Transient increases in blood pressure arising soon after treatment. flushing	-	Hypotension, Raynaud's syndrome
Respiratory, thoracic and mediastinal disorders	Dyspnoea	-	-
Gastrointestinal disorders	Nausea and vomiting***	-	Ischaemic colitis, diarrhoea, dysphagia
Skin and subcutaneous tissue disorders	-	-	Hyperhidrosis
Musculoskeletal and connective tissue disorders	Myalgia	-	Neck stiffness, arthralgia

General disorders and administration site conditions	Pain, sensations of heat or cold, pressure or tightness (these events are usually transient and may be intense and affect any part of the body including the chest and throat). Feelings of weakness, fatigue (both events are mostly mild to moderate in intensity and transient)		Pain trauma activated, pain inflammation activated
Investigations	-	Minor disturbances in liver function tests have occasionally been observed	-

*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.
**Visual disorders may also occur during a migraine attack itself.
***Occurred in some patients but it is unclear if this is related to Sumatriptan or the underlying condition.

Organ System	Very Common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders	-	-	-	-	eosinophilia, thrombocytopenia, leucopenia, pancytopenia, haemolytic anaemia, aplastic anaemia, agranulocytosis	-
Immune system disorders	-	-	-	Hypersensitivity reactions, anaphylactic reaction, angioneurotic oedema	-	-
Metabolism and nutrition disorders	-	-	Hyperkalemia, fluid retention	-	-	-
Psychiatric disorders	-	-	Mood changes, depression, impaired ability to concentrate, cognitive disorder, insomnia, sleep disorder	-	-	-
Nervous system disorders	-	Headache, dizziness, lightheadedness	Convulsions	-	Aseptic meningitis, worsening of Parkinson's disease	-
Eye disorders	-	Visual disturbances	-	-	-	-
Ear and labyrinth disorders	-	Tinnitus, hearing disorders	-	Hearing loss	-	-
Cardiac disorders*	-	Worsening of heart failure (oedema, dyspnoea)	Palpitations	-	-	-
Vascular disorders*	-	-	-	-	Vasculitis	-

Respiratory, thoracic and mediastinal disorders	-	-	-	Pulmonary oedema, worsening of asthma	Eosinophilic pneumonitis	-
Gastrointestinal disorders**	Upper abdominal pain, heartburn, nausea, constipation	Stomatitis, diarrhoea, vomiting, dyspepsia	Gastrointestinal ulcers, haemorrhages and/or perforations, haematemesis, melaena, exacerbation of ulcerative colitis and Crohn's disease	-	Sialadenitis, pancreatitis	-
Hepatobiliary disorders	-	-	Elevated liver enzyme levels, Jaundice	Toxic hepatitis	-	-
Skin and subcutaneous tissue disorders	-	Pruritus, skin rashes, urticaria, increased sweating, purpura, ecchymosis	-	Hair loss, photosensitivity, pseudoporphyria	Exacerbation of lichen planus, exacerbation of erythema nodosum, exacerbation of lupus erythematosus disseminatus (SLE), toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome.	Drug reaction witheosinophilia and systemic symptoms (DRESS) (see section 4.4), fixed drug eruption
Musculoskeletal and connective tissue disorders	-	-	-	Myalgia muscle weakness	-	-

Renal and urinary disorders	-	-	-	-	Haematuria, renal failure, glomerulonephritis, interstitial nephritis, nephrotic syndrome, papillary necrosis.	-
Reproductive system and breast disorders	-	-	Menstrual disorders	-	-	-
General disorders and administration site disorders	-	Tiredness	Thirst	-	-	Pyrexia

Other Events Observed in Migraine Clinical Trials Associated with the Administration of Naproprym S:

The occurrence of less commonly reported adverse clinical events is presented in this section. Because the reports include events observed in an open-label, long-term safety study in which Naproprym S was used as needed for up to 12 months, the role of Naproprym S cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used Naproprym S and reported an event divided by the total number of patients (N = 3,302) exposed to Naproprym S. Events listed in the previous table and text are not included below. Those events described too generally to be informative or those unlikely to be associated with the use of Naproprym S are excluded. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are those occurring in at least 1/100 patients, infrequent adverse events are those occurring in 1/100 to 1/1,000 patients, and rare adverse events are those occurring in fewer than 1/1,000 patients.

Common

Nervous system disorders: Dizziness, Somnolence, Paresthesia

Gastrointestinal disorders: Nausea, Dyspepsia, Dry mouth

Pain and other pressure sensations: Chest discomfort/chest pain, Neck/throat/jaw pain/tightness/pressure

Less Common

Blood and Lymphatic Disorders: Infrequent was lymphadenopathy. Rare were anemia, ecchymosis, leukopenia.

Cardiac Disorders: Infrequent was tachycardia. Rare were acute coronary syndrome, cardiac flutter, congestive cardiac failure, right ventricular failure, ventricular extrasystoles.

Ear and Labyrinth Disorders: Infrequent were ear pain, tinnitus. Rare were motion sickness, vertigo.
Endocrine, Metabolic, and Nutrition Disorders: Rare were diabetes mellitus, goiter, hypoglycemia, hypothyroidism.
Eye Disorders: Infrequent was conjunctivitis. Rare were cataract, conjunctival hemorrhage, visual disturbance.
Gastrointestinal Disorders: Frequent was abdominal pain. Infrequent were abdominal distention, constipation, diarrhea, dysgeusia, dysphagia, flatulence, gastritis, gastroesophageal reflux disease, vomiting. Rare were colitis, diverticulitis, gastric ulcer, irritable bowel syndrome, oral mucosal blistering, swollen tongue.
General Disorders: Frequent was fatigue. Infrequent were feeling jittery, lethargy, malaise, peripheral edema, pyrexia, temperature intolerance, thirst. Rare was difficulty in walking.

Hepatobiliary Disorders: Rare was biliary colic.
Infections and Infestations: Rare were kidney infection, pneumonia, sepsis, staphylococcal infection, viral myocarditis.
Musculoskeletal and Connective Tissue: Infrequent were arthralgia, back pain, muscular weakness, myalgia, sensation of heaviness.
Nervous System Disorders: Infrequent were burning sensation, disturbance of attention, insomnia, mental impairment, tremor. Rare were aphasia, facial palsy, impairment of psychomotor skills, sedation.
Psychiatric Disorders: Infrequent were anxiety, depression, irritability, nervousness. Rare were disorientation, panic attack.
Renal and Urinary Disorders: Infrequent was nephrolithiasis. Rare was renal insufficiency.
Respiratory, Thoracic, and Mediastinal: Infrequent were asthma, cough, dyspnea, oropharyngeal swelling. Rare was pleurisy.
Skin and Subcutaneous Disorders: Infrequent were facial swelling, hyperhydrosis, pruritus, rash, urticaria. Rare was systemic lupus erythematosus.
Vascular Disorders: Infrequent were flushing, hot flush, hypertension. Rare were epistaxis, peripheral coldness.

4.9. Overdose

Patients have received single oral doses of 140 to 300 mg of Sumatriptan without significant adverse effects. 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. Significant Naproxen overdosage may be characterized by lethargy, dizziness, drowsiness, epigastric pain, abdominal discomfort, heartburn, indigestion, nausea, transient alterations in liver function, hypoprothrombinemia, renal dysfunction, metabolic acidosis, apnea, disorientation, or vomiting. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression, and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose. Because Naproxen may be rapidly absorbed, high and early blood levels should be anticipated. A few patients have experienced seizures, but it is not clear whether or not these were drug related. It is not known what dose of the drug would be life threatening.

In animals 0.5 g/kg of activated charcoal was effective in reducing plasma levels of Naproxen.
Patients should be managed by symptomatic and supportive care. There are no specific antidotes.
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.
Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose.
Forced diuresis, alkalinization of urine, or hemoperfusion may not be useful due to high protein binding.

5. Pharmacological properties

5.1. Mechanism of action

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.
Naproprym-S has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of Naproprym-S, 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.

5.2. Pharmacodynamic properties

Sumatriptan and Naproxen contains Sumatriptan, a 5-HT1 receptor agonist that mediates vasoconstriction of the human basilar artery and vasculature of human dura mater, which correlates with the relief of migraine headache. It also contains Naproxen, an NSAID that inhibits the synthesis of inflammatory mediators. Therefore, Sumatriptan and Naproxen contribute to the relief of migraine through pharmacologically different mechanisms of action. Sumatriptan is a 5-HT1 receptor agonist that binds with high affinity to 5-HT1B and 5-HT1D receptors. Sumatriptan has only a weak affinity for 5-HT1A, 5-HT5A, and 5-HT7 receptors and no significant affinity (as measured using standard radioligand binding assays) or pharmacological activity at 5-HT2, 5-HT3, or 5-HT4 receptor subtypes or at alpha1-, alpha2-, or beta-adrenergic; dopamine1; dopamine2; muscarinic; or benzodiazepine receptors. In addition to causing vasoconstriction, experimental data from animal studies show that Sumatriptan also activates 5-HT1 receptors on peripheral terminals of the trigeminal nerve innervating cranial blood vessels. Such an action may contribute to the antimigrainous effect of Sumatriptan in humans. In the anesthetized dog,

Sumatriptan selectively reduces carotid arterial blood flow with little or no effect on arterial blood pressure or total peripheral resistance.

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

5.3. Pharmacokinetic properties

Sumatriptan and Naproxen is a formulation of 85 mg of Sumatriptan and 500 mg of Naproxen with a distinct pharmacokinetic profile. Cmax (median, range) for Sumatriptan following administration of Sumatriptan and Naproxen occurs at approximately 1 hour (0.3 to 4.0 hours). Cmax (median, range) for Naproxen following administration of Sumatriptan and Naproxen occurs at approximately 5 hours (0.3 to 12 hours). The Sumatriptan half-life is approximately 2 hours (15% to 43% CV) and the Naproxen half-life is approximately 19 hours (13% to 15% CV).

Absorption and Bioavailability: Bioavailability of Sumatriptan is approximately 15%, primarily due to presystemic (first-pass) metabolism and partly due to incomplete absorption. Naproxen is rapidly and completely absorbed from the gastrointestinal tract with an in vivo bioavailability of 95%.

Food Effects: Food had no significant effect on the bioavailability of Sumatriptan or Naproxen administered as Sumatriptan and Naproxen, but slightly delayed the Tmax of Sumatriptan by about 0.6 hour. These data indicate that Sumatriptan and Naproxen may be administered without regard to food.

Distribution: The volume of distribution of Sumatriptan is 2.4 L/kg. Plasma protein binding is 14% to 21%. The effect of Sumatriptan on the protein binding of other drugs has not been evaluated, but would be expected to be minor, given the low protein binding. 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: 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. In vitro studies with human microsomes suggest that Sumatriptan is metabolized by monoamine oxidase (MAO), predominantly the A isoenzyme, and inhibitors of that enzyme may alter Sumatriptan pharmacokinetics to increase systemic exposure. 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: Radiolabeled 14C-Sumatriptan administered orally is largely renally excreted (about 60%), with about 40% found in the feces. The elimination half-life of Sumatriptan is approximately 2 hours. 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 3 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.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Corneal Opacities Dogs receiving oral Sumatriptan developed corneal opacities and defects in the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2mg/kg/day, and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a 60week study. Earlier examinations for these toxicities were not conducted and no-effect doses were not established. The lowest dose tested is less than the MHDD (170mg) of Sumatriptan on a mg/m^2 basis.

7. Description

Yellow coloured, capsule shaped, biconvex, film coated tablet with break line on one side.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Refer pack

8.3. Packaging information

Alu Blister pack of 2 Tablets

8.4. Storage and handling instructions

Store at a temperature not exceeding 30ºC.

9. Patient Counselling Information

Inform patients, families, or their caregivers of the following information before initiating therapy with Naproprym-S and periodically during the course of ongoing therapy.

Advise patients to be alert for the symptoms of cardiovascular thrombotic effects such as myocardial infarction or stroke, which may result in hospitalization and even death. Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding. Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea, jaundice, right upper quadrant

tenderness, and “flu-like” symptoms). Inform patients that anaphylactic reactions have occurred in patients receiving the components of Naproprym-S. Inform patients that Naproprym-S, like other NSAID-containing products, may increase the risk of serious skin side effects such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, which may result in hospitalizations and even death. This molecule should not be used during the third trimester of pregnancy because NSAID-containing products have been shown to cause premature closure of the ductus arteriosus. Advise patients to notify their healthcare provider if they are breastfeeding or plan to breastfeed. Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur. Use of Naproprym-S within 24 hours of another triptan or an ergot-type medication (including dihydroergotamine or methysergide) is contraindicated. Caution patients about the risk of serotonin syndrome with the use of Naproprym-S or other triptans, particularly during concomitant use with SSRIs, SNRIs, TCAs, and MAO inhibitors. Treatment with Naproprym-S may cause somnolence and dizziness; instruct patients to evaluate their ability to perform complex tasks after administration of Naproprym-S. Advise patients with preexisting asthma to seek immediate medical attention if their asthma worsens after taking Naproprym-S.

10. Details of manufacturer

Manufactured by:
Tirupati Medicare Limited
Nahan Road, Paonta Sahib, Dist. Sirmour 173025 HP, India

Marketed by:
Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 3 & 11 to 13 Ground Floor,
101 to 106 & 111 to 116 First Floor, 201 to 206 & 211 to 216 2nd Floor,
Pimplas, Dist. Thane, Bhiwandi-421 302, Maharashtra, India.

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11. Details of Permission or license number with date

MNB/07/552 dated 17-May-22

12. Date of revision

Version 1.0 dated 6-Jun-25

For product complaints and queries please write to webmasterindia@abbott.com