Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
SYNFLEX-M 85mg+500mg Tablets

2. Qualitative and quantitative composition
Each film coated tablet contains:
Sumatriptan Succinate (USP) eq. to Sumatriptan.....85mg
Naproxen Sodium (USP).....500mg
For a full list of excipients, see section 6.1.

3. Pharmaceutical form
Film-coated tablet.

Blue oblong-shaped, biconvex film-coated tablet, engraved M/D on one side and plain on the other side.

4. Clinical particulars
4.1 Therapeutic indications
SYNFLEX-M is indicated for the acute treatment of migraine with or without aura in adults and paediatric 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 SYNFLEX-M, reconsider the diagnosis of migraine before SYNFLEX-M is administered to treat any subsequent attacks.
- SYNFLEX-M is not indicated for the prevention of migraine attacks.
- Safety and effectiveness of SYNFLEX-M have not been established for cluster headache.

4.2 Posology and method of administration
Administration Information:
SYNFLEX-M may be administered with or without food. Tablets should not be split, crushed, or chewed.
Adults:
The recommended dosage for adults is 1 tablet of SYNFLEX-M 85/500mg. SYNFLEX-M 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 SYNFLEX-M 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.

Paediatric Patients Aged 12 to 17 Years:
The recommended dosage for pediatric patients 12 to 17 years of age is 1 tablet of SYNFLEX-M 10/60 mg.
The maximum recommended dosage in a 24-hour period is 1 tablet of SYNFLEX-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.
Dosage in Individuals with Hepatic Impairment:
SYNFLEX-M is contraindicated in patients with severe hepatic impairment. Use the lowest effective dosage for the shortest duration consistent with individual treatment goals.

4.3 Contraindications

SYNFLEX-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.
- 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 SYNFLEX-M
- Third trimester of pregnancy
- Severe hepatic impairment

4.4 Special warnings and precautions for use

Cardiovascular Thrombotic Events:
The use of SYNFLEX-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.
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. SYNFLEX-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.
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 [see Warnings and Precautions (5.2)].
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 [see Contraindications (4)].
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 SYNFLEX-M. If there is evidence of CAD or coronary artery vasospasm, SYNFLEX-M is contraindicated. For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administering the first dose of SYNFLEX-M in a medically supervised setting and performing an electrocardiogram (ECG) immediately following administration of SYNFLEX-M. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of SYNFLEX-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 SYNFLEX-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.

Among 3,302 adult patients with migraine who received SYNFLEX-M 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 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 SYNFLEX-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 SYNFLEX-M if these disturbances occur. SYNFLEX-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 SYNFLEX-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 SYNFLEX-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. SYNFLEX-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 SYNFLEX-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 SYNFLEX-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. SYNFLEX-M is contraindicated in patients with severe hepatic impairment [see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]. 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 SYNFLEX-M. SYNFLEX-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 SYNFLEX-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 SYNFLEX-M. This occurrence has included patients without a history of hypertension.

NSAIDs, including naproxen, a component of SYNFLEX-M, can also lead to onset of new hypertension or worsening of pre-existing 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 [see Drug Interactions (7)].

Monitor blood pressure in patients treated with SYNFLEX-M. SYNFLEX-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]) [see Drug Interactions (7)].

Avoid the use of SYNFLEX-M in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If SYNFLEX-M is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

Since each SYNFLEX-M 85/500 mg tablet contains approximately 60 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.

Serotonin Syndrome:

Serotonin syndrome may occur with SYNFLEX-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 SYNFLEX-M if serotonin syndrome is suspected.

Renal Toxicity and Hyperkalemia:

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

SYNFLEX-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 SYNFLEX-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 SYNFLEX-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 SYNFLEX-M. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of SYNFLEX-M [see Drug Interactions (7)]. Avoid the use of SYNFLEX-M in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If SYNFLEX-M is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

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 SYNFLEX-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. SYNFLEX-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. SYNFLEX-M is contraindicated in

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

Premature Closure of the Ductus Arteriosus:

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

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

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

When SYNFLEX-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. SYNFLEX-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 SYNFLEX-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.

4.5 Interaction with other medicinal products and other forms of interaction

Clinically significant drug interactions with NSAID's 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 SYNFLEX-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 SYNFLEX-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 SYNFLEX-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 SYNFLEX-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:	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:	Concomitant use of SYNFLEX-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 SYNFLEX-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 SYNFLEX-M and ACE-inhibitors, ARBs, or beta- blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of SYNFLEX-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 SYNFLEX-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 SYNFLEX-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 SYNFLEX-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 SYNFLEX-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 SYNFLEX-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.
Pemetrexed	
Clinical Impact:	Concomitant use of NSAIDs and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Intervention:	During concomitant use of SYNFLEX-M 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	
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 SYNFLEX-M when given concurrently with probenecid.

4.6 Fertility, 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. SYNFLEX-M (sumatriptan and naproxen) should be used during the first and second trimester of pregnancy only if the potential benefit justifies the potential risk to the foetus. SYNFLEX-M 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.
Oral administration of sumatriptan combined with naproxen sodium (5/9, 25/45, or 50/90 mg/kg/day sumatriptan/naproxen sodium) or each drug alone (50/0 or 0/90 mg/kg/day sumatriptan/naproxen sodium) to pregnant rabbits during the period of organogenesis resulted in increased total incidences of fetal abnormalities at all doses and increased incidences of specific malformations (cardiac interventricular septal defect in the 50/90 mg/kg/day group, fused caudal vertebrae in the 50/0 and 0/90 mg/kg/day groups) and variations (absent intermediate lobe of the lung, irregular ossification of the skull, incompletely ossified sternal centra) at the highest dose of sumatriptan and naproxen alone and in combination. A no-effect dose for developmental toxicity in rabbits was not established. The lowest effect dose was 5/9 mg/kg/day sumatriptan/naproxen sodium, which was associated with plasma exposures (AUC) to sumatriptan and naproxen that were less than those attained at the maximum human daily dose (MHDD) of 170 mg sumatriptan and 1000 mg naproxen sodium (two tablets of SYNFLEX-M 85/500 mg in a 24-hour period).
In previous developmental toxicity studies of sumatriptan, oral administration to pregnant rats during the period of organogenesis resulted in an increased incidence of fetal blood vessel abnormalities and decreased pup survival at doses of 250 mg/kg/day or higher. The highest no-effect dose was 60 mg/kg/day, which is approximately 3 times the MHDD of 170 mg sumatriptan on a mg/m2 basis. Oral administration of sumatriptan to pregnant rabbits during the period of organogenesis resulted in increased incidences of vascular and skeletal abnormalities at a dose of 50 mg/kg/day and embryolethality at 100 mg/kg/day. The highest no-effect dose of sumatriptan for developmental toxicity in rabbits was 15 mg/kg/day, or approximately 2 times the MHDD of 170 mg sumatriptan on a mg/m2 basis.
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.
Lactation:
Both active components of SYNFLEX-M, sumatriptan and naproxen, have been reported to be secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from SYNFLEX-M, 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.

4.7 Effects on ability to drive and use machines.

No studies on the effect on the ability to drive and use machines have been performed. Drowsiness may occur as a result of migraine or treatment with sumatriptan. This may influence the ability to drive and to operate machinery.

4.8 Undesirable effects

The following serious adverse reactions have been recorded and are described in more detail in section 4.4:

- 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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Pharmacy and Poisons Board website (https://pv.pharmacyboardkenya.org).

4.9 Overdose

Patients have received single oral doses of 140 to 300 mg of sumatriptan without significant adverse effects. Volunteers have received single oral doses of 140 to 400 mg without serious adverse events.

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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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.

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

Blood Pressure:

In a randomized, double-blind, parallel group, active control trial, Sumatriptan/Naproxen 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.

5.2 Pharmacokinetic properties

Absorption and Bioavailability:

Sumatriptan when given as SYNFLEX-M 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 SYNFLEX-M 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 SYNFLEX-M 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 SYNFLEX-M 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 SYNFLEX-M 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 SYNFLEX-M, 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.

he 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.

Specific Populations

Geriatrics

The pharmacokinetics of SYNFLEX-M 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 and Naproxen 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 and Naproxen 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 and Naproxen 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 and Naproxen 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 and Naproxen 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.

5.3 Preclinical safety data

Carcinogenesis

The carcinogenetic potential of this drug combination has not been studied.

In carcinogenicity studies in mouse and rat, sumatriptan was administered orally for 78 and 104 weeks, respectively, at doses up to 160 mg/kg/day. The highest doses tested are approximately 5 (mouse)

and 9 (rat) times the maximum human daily dose (MHDD) of 170 mg sumatriptan on a mg/m2 basis.
The carcinogenic potential of naproxen was evaluated in a 2-year oral carcinogenicity study in rats at doses of 8, 16, and 24 mg/kg/day and in another 2-year oral carcinogenicity study in rats at a dose of 8 mg/kg/day. No evidence of tumorigenicity was found in either study. The highest dose tested is less than the MHDD (1000 mg) of naproxen, on a mg/m2 basis.
Mutagenesis
Sumatriptan and naproxen sodium tested alone and in combination were negative in an in vitro bacterial reverse mutation assay, and in an in vivo micronucleus assay in mice. The combination of sumatriptan and naproxen sodium was negative in an in vitro mouse lymphoma tk assay in the presence and absence of metabolic activation. However, in separate in vitro mouse lymphoma tk assays, naproxen sodium alone was reproducibly positive in the presence of metabolic activation.
Naproxen sodium alone and in combination with sumatriptan was positive in an in vitro clastogenicity assay in mammalian cells in the presence and absence of metabolic activation. The clastogenic effect for the combination was reproducible within this assay and was greater than observed with naproxen sodium alone. Sumatriptan alone was negative in these assays.
Chromosomal aberrations were not induced in peripheral blood lymphocytes following 7 days of twice-daily dosing with sumatriptan and naproxen in human volunteers.
In previous studies, sumatriptan alone was negative in in vitro (bacterial reverse mutation [Ames], gene cell mutation in Chinese hamster V79/HGPRT, chromosomal aberration in human lymphocytes) and in vivo (rat micronucleus) assays.
Impairment of Fertility
The effect of sumatriptan and naproxen on fertility in animals has not been studied.
When sumatriptan (5, 50, 500 mg/kg/day) was administered orally to male and female rats prior to and throughout the mating period, there was a drug-related decrease in fertility secondary to a decrease in mating in animals treated with doses greater than 5 mg/kg/day (less than the MHDD of 170 mg on a mg/m2 basis). It is not clear whether this finding was due to an effect on males or females or both.
Animal Toxicology: Corneal Opacities
Dogs receiving oral sumatriptan developed corneal opacities and defects in the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2 mg/kg/day, and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a 60- week 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 (170 mg) of sumatriptan on a mg/m2 basis.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline Cellulose M 101
Dicalcium Phosphate dihydrous DC grade
Sodium Croscarmellose Type A
Povidone K-30
Sodium Bicarbonate
Talc
Magnesium stearate
Sheffcoat White 5Y00065
Indigo Carmine 85%

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage:

Store below 30℃.

6.5 Nature and contents of container

SYNFLEX-M is supplied in the following dosage form, strength & pack size:

Tablets 85mg+500mg 2's, 6's, 10's

6.6 Special precautions for disposal and other handling:

No special requirements.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:

MARTIN DOW LIMITED
Plot No. 37,
Sector 19,
Korangi industrial area,
Karachi-74900, Pakistan

Manufacturing site address:

MARTIN DOW LIMITED
Plot No. 37,
Sector 19,
Korangi industrial area,
Karachi-74900, Pakistan

8. Marketing authorization number

CTD9852

9. Date of first registration

29/03/2023

10. Date of revision of the text:

15/09/2023.

11. Dosimetry:

Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:
Not Applicable