SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Synflex- M 85mg+500mg Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:
Sumatriptan Succinate (USP) eq. to Sumatriptan...85mg
Naproxen Sodium (USP)……..……500mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute treatment of migraine with or without aura in adults & pediatrics 12 years of age & older.

Limitations of Use:

- Use only if a clear diagnosis of migraine headache has been made. If there is no response, reconsider diagnosis before treating for subsequent attacks.
- Not indicated for prevention of migraine attacks.
- Safety & effectiveness of Synflex-M is not known for cluster headache.

4.2 Posology and method of administration

Dosage in Adults

1 tablet of Synflex-M. The choice of the dose of sumatriptan, & of the use of a fixed combination should be made on an individual basis, weighing possible benefit of higher dose of sumatriptan with the potential for greater risk of adverse reactions.
Max. recommended dose: 2 tablets/day, 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 is not known. May be administered with or without food. Tablets should not be split, crushed, or chewed.

Dosage in 12 to 17 Years of Age

1 tablet of Synflex-M in 24 hour period. The safety of treating an average of more than 2 migraine headaches in pediatric individuals in a 30-day period is not known.

Dosing in Individuals with Hepatic Impairment

Contraindicated in severe hepatic impairment. Use the lowest effective dosage for the shortest duration consistent with individual treatment goals.

4.3 Contraindications

Ischemic CAD or coronary artery vasospasm, including prinzmetal's angina, in the setting of CABG surgery, WPW syndrome or other arrhythmias, history of stroke or TIA or history of hemiplegic or basilar migraine, peripheral vascular disease, ischemic bowel disease, uncontrolled hypertension, recent use of ergotamine-containing, ergot-type medication or another 5-hydroxytryptamine1 agonist, concurrent or recent use of a MAO-A inhibitor, history of asthma, urticaria, or allergic-type

reactions after taking aspirin or other NSAIDs, known hypersensitivity to any component of combination, 3rd trimester of pregnancy and severe hepatic impairment.

4.4 Special warnings and precautions for use

- Serious cardiac adverse reactions may occur, including acute MI, occurring within a few hours following administration of sumatriptan with or without a history. Sumatriptan+naproxen may cause coronary artery vasospasm, even in individuals without a history of CAD.
- With all NSAIDs there may be an increased risk of serious CV thrombotic events, including MI & stroke, which can be fatal. Individuals with known CV disease or risk factors are at higher risk. Use lowest effective dose for shortest duration possible.
- The individuals treated with NSAIDs in the post- MI period are known to be at increased risk of re-infarction, CV-related death & all-cause mortality. Consider periodic CV evaluation & remain alert for signs/ symptoms of serious CV events.
- NSAIDs, including naproxen may cause serious GI adverse events including inflammation, bleeding, ulceration, & perforation of the stomach, small intestine, or large intestine, which can be fatal.
- Individuals with a history of PUD &/or GI bleeding on NSAIDs have a >10-fold risk for GI bleeding compared to no history. Other risk factors include longer therapy; concomitant corticosteroids, aspirin, anticoagulants, or SSRIs; smoking; alcohol; elderly; & poor health. Fatal GI events may occur in elderly or debilitated & individuals with advanced liver disease &/or coagulopathy.
- Life-threatening disturbances of cardiac rhythm, including VT & VF leading to death, is known to occur within a few hours following administration of 5-HT agonists. Discontinue drug if this occurs.
- Sensations of tightness, pain, pressure, & heaviness in the precordium, throat, neck, & jaw commonly occur after treatment with sumatriptan & are usually non-cardiac in origin. Perform cardiac evaluation in high risk individuals.
- Cerebral hemorrhage, SAH, & stroke may occur in individuals treated with 5-HT agonists, & some may result in fatalities. Discontinue sumatriptan + naproxen if such event occurs. With no past-history of migraine, exclude other potentially serious neurological conditions.
- Sumatriptan may cause peripheral vascular ischemia, GI vascular ischemia & infarction, splenic infarction, & Raynaud's syndrome. Transient & permanent blindness & significant partial vision loss may occur with the use of 5-HT agonists.
- Borderline elevations of 1 or more liver tests may occur in up to 15% of individuals who take NSAIDs including naproxen. 3 times ULN elevations of ALT or AST may occur in approx.1% of individuals with NSAIDs. In addition, rare, sometimes fatal cases of severe hepatic injury, jaundice & fatal fulminant hepatitis, liver necrosis & failure may also occur.
- Significant elevation in blood pressure, including hypertensive crisis with acute impairment of organ systems, rarely may occur with 5-HT agonists use, including sumatriptan. NSAIDs, including naproxen, may also lead to new onset hypertension or worsening of pre-existing hypertension, which may contribute to increased incidence of CV events. Individuals taking ACEI, ARBs, beta-blockers, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs. Monitor their BP.
- NSAID use may increase the risk of MI, hospitalization for heart failure & death. Use of naproxen may blunt the CV effects of several therapeutic agents used to treat these conditions. Avoid the use of sumatriptan+ naproxen in individuals with severe HF unless the benefits outweigh risk. Monitor for signs of worsening heart failure. Since each sumatriptan + naproxen sodium 85/500mg tablet contains approx. 60mg sodium, consider this in whom intake of sodium must be severely restricted.

- Overuse of acute migraine drugs may lead to exacerbation of headache. Detoxification, withdrawal of the overused drugs, & treatment of withdrawal symptoms may be necessary.
- Serotonin syndrome may occur with sumatriptan+ naproxen sodium, particularly during coadministration with SSRIs, SNRIs, TCAs & MAO inhibitors. If suspected, discontinue the drug.
- Long-term use of NSAIDs may result in renal papillary necrosis & other renal injury. Higher risk is in impaired renal function, dehydration, hypovolemia, HF, liver dysfunction, salt depletion, those taking diuretics & ACEI or ARBs & elderly. Discontinue drug in such case. Not recommended for use in these patients & monitor if used. Correct the volume status in dehydrated or hypovolemic before initiating drug.
- Hyperkalemia, may occur with the use of NSAIDs, even in some individuals without renal impairment.
- Anaphylactic reactions may occur without known prior exposure to either component of sumatriptan + naproxen. This can be life-threatening or fatal. Do not give in aspirin triad (see contraindications).
- NSAID-containing products can cause serious skin adverse reactions such as exfoliative dermatitis, SJS & TEN which can be fatal. Discontinue at the first sign of hypersensitivity.
- Sumatriptan + naproxen may cause premature closure of the ductus arteriosus. Avoid use of NSAIDs in pregnant women in third trimester.
- NSAIDs may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant warfarin use, other anti-coagulants, anti-platelet agents, SSRIs & SNRIs may increase this risk. Monitor these individuals.
- Causing when using in pre-existing asthma. If used in pre-existing asthma (without known aspirin sensitivity, see contraindications), monitor for changes in the signs & symptoms.
- Seizures are known to occur following administration of sumatriptan. Some may occur in individuals with either a history of seizures, concurrent conditions predisposing to seizures or even with no apparent factors. Use with caution.
- Sumatriptan + naproxen sodium may reduce inflammation, & possibly fever & diminish the utility of diagnostic signs in detecting infections.
- Monitoring individuals on long-term NSAID treatment with a CBC & a chemistry profile periodically.

4.5 Interaction with other medicinal products and other forms of interaction Concomitant use is contraindicated with:

Clinically significant interactions with naproxen or sumatriptan

- Ergot-containing drugs & 5-HT agonist drugs may cause prolonged vasospastic reactions (see contraindications).
- MAO-A inhibitors increase systemic exposure of oral sumatriptan by 7-fold, thus, contraindicated. Monitor for bleeding when concomitant use of with anti-coagulants, anti-platelets, SSRIs & SNRIs.
- No greater therapeutic effect is known with concomitant use of aspirin, than NSAID alone. Concomitant use may increase bleeding risk.
- Serotonin syndrome may occur during coadministration of triptans & SSRIs, SNRIs, TCAs, & MAOI. Discontinue drug if suspected.
- NSAIDs may diminish the antihypertensive effect of ACEI, ARBs or β-blockers. In the elderly, volume-depleted, or renal impaired, co-administration may result in deterioration of renal function, including possible ARF. These effects are usually reversible.

- NSAIDs may reduce the natriuretic effect of loop & thiazide diuretics. During concomitant use observe individuals for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects.
- Concomitant use with digoxin may increase the serum concentration & half-life of digoxin. Monitor digoxin levels.
- NSAIDs have produced elevations in plasma lithium levels (~15%) & reductions in renal lithium clearance (~20%). During concomitant use monitor individuals for signs of lithium toxicity.
- Concomitant therapy with methotrexate may prolong its serum levels, resulting in deaths from severe hematologic & GI toxicity. On use, monitor for methotrexate toxicity.
- Concomitant use of NSAIDs & cyclosporine may increase cyclosporine nephrotoxicity. Monitor for signs of worsening renal function.
- Concomitant use of NSAIDs & salicylates may increase risk of GI toxicity. It is not recommended.
- Concomitant use may increase the risk of pemetrexed-associated myelosuppression, renal, & GI toxicity. Monitor for this in renally impaired.
- Probenecid given concurrently increases naproxen anion plasma levels & may extend plasma half-life significantly. Reduce frequency of administration of sumatriptan + naproxen.
- Naproxen may decrease platelet aggregation & prolong bleeding time. It may also result in increased urinary values for 17-ketogenic steroids. Temporarily discontinue naproxen 72 hours before adrenal function tests.

4.6 Fertility, pregnancy and lactation

Pregnancy, Labour, Delivery and Lactation
Pregnancy Category C. During the first two trimesters & Category X, during the third trimester. Not recommended in labor & delivery. Both active components of sumatriptan + naproxen are known to be secreted in human milk. Decision should be made whether to discontinue nursing or the drug.

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

Cardiovascular Thrombotic Events, GI Bleeding, Ulceration & Perforation, Arrhythmias, Chest, Throat, Neck, &/or Jaw Pain/Tightness/Pressure, Cerebrovascular events, Other vasospasm reactions, Hepatotoxicity, Hypertension, Heart failure & Edema, Medication overuse, Headache, Renal toxicity & Hyperkalemia, Anaphylactic reactions, Serious skin reactions, Hematological toxicity, Exacerbation asthma related to aspirin sensitivity, Seizures, Dizziness, Somnolence; Paresthesia, Nausea, Dyspepsia, Dry mouth, Chest discomfort/chest pain, Hot flashes and Muscle tightness.

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 email productsafety@martindow.com.

4.9 Overdose

Symptoms following acute NSAID overdosages include lethargy, drowsiness, nausea, vomiting & epigastric pain. Gl bleeding may occur. Manage individuals with symptomatic & supportive care following overdosage. There are no specific antidotes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

Sumatriptan binds with high affinity to cloned 5-HT1B/1D receptors. Naproxen is an inhibitor of prostaglandin synthesis. Combination has analgesic, anti-inflammatory & anti-pyretic properties.

Pharmacodynamics

Significant elevation in BP may occur with 5-HT agonists & NSAIDs in individuals with & without a history of hypertension.

5.2 Pharmacokinetic properties

Absorption & Bioavailability

The mean Cmax of combination is known to be similar to that of sumatriptan succinate 100mg tablets alone & median Tmax is 1 hour (range: 0.3 to 4.0 hours). Naproxen, as combination, has Cmax which is approximately 36% lower than naproxen sodium 550mg tablets & a median Tmax of 5 hours (range: 0.3 to 12 hours). AUC values may be similar for the combination & both drugs alone. Bioavailability of sumatriptan is approx. 15% & for naproxen is 95%. Food is not known to have significant effect on the bioavailability but may slightly delay the Tmax of sumatriptan by about 0.6 hour.

Distribution

Plasma protein binding is known to be 14% to 21%. The volume of distribution of sumatriptan may be 2.7L/kg & that of naproxen is 0.16L/kg. At therapeutic levels naproxen may be >99% albumin bound.

Metabolism

Sumatriptan is metabolized by MAO predominantly the A-isoenzyme. No significant effect may be seen with MAO-B inhibitor. Naproxen is extensively metabolized to 6-0-desmethyl naproxen.

Elimination

Elimination half-life of sumatriptan is ~2 hours. Renal excretion maybe 60% & fecal 40%. The clearance of naproxen is known to be 0.13mL/min/kg. Approx. 95% of the naproxen is excreted in the urine, primarily as naproxen (<1%), 6-0-desmethyl naproxen (<1%), or their conjugates (66% to 92%). The plasma half-life of the naproxen anion is ~19 hours. The corresponding half-lives of both metabolites & conjugates of naproxen is known to be <12hrs. In renal failure, metabolites may accumulate.

Specific Populations

<u>Geriatrics</u>

Pharmacokinetics of combination is unknown. For oral sumatriptan, it is similar in elderly & young. Unbound plasma fraction (<1%) may increase in elderly.

<u>Pediatrics</u>

The AUC & Cmax of sumatriptan may be 50-60% higher following a single dose of 10/60mg in children 12 to 17 years of age compared with adult individuals, & may be 6-26% higher following a single dose of 30/180mg or 85/500mg in pediatrics than adults. Naproxen pharmacokinetics may be similar in both.

Renal & Hepatic Impairment

Not known. Individuals with hepatic impairment are known to have an approx. 70% increase in AUC & Cmax of sumatriptan & a Tmax 40min earlier compared to healthy individuals. Potential exists for naproxen metabolites to accumulate in renal insufficiency.

5.3 Preclinical safety data

No preclinical study is known with the moxifloxacin.

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%
- DI Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

- Nature of content
  PVC /PVDC Al. Foil Blister

- Contents of the pack

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

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

083167

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorization: 15-03-2017

Renewal of the Authorization: 16-03-2022