Summary of product characteristics (SmPC)

1. Name of the medicinal product

SUMO-PLUS

2. Qualitative and quantitative composition

Each film coated tablet contains:

Etoricoxib	60 mg
Paracetamol BP	325 mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film coated Tablet

White colour round shape biconvex film coated tablet with both side plain.

4. Clinical Particulars

4.1 Therapeutic Indications

SUMO-PLUS Tablets are a combination medicine used for the treatment of painful muscle spasm associated with musculoskeletal conditions.

4.2 Posology and Method of Administration

One tablet to be taken with food, two or three times

daily. Tablets should be swallowed whole, not

chewed.

4.3 Contraindication

SUMO-PLUS Tablets are contraindicated in patients with the following conditions:

- Hypersensitivity to Etoricoxib and/ or paracetamol other constituents.
- Patients with active peptic ulcer/haemorrhage or perforation or who have active GI bleeding or other active bleedings, e.g. cerebrovascular bleedings.
- Pregnant women and in women planning a pregnancy.
- Women of childbearing potential who are not using effective contraception

- Patients with a known hypersensitivity to Etoricoxib, acetylsalicylic acid, other NSAIDs, misoprostol, other prostaglandins, or any other ingredient of the product.
- Patients in whom attacks of asthma, urticaria or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs.
- Treatment of peri-operative pain in the setting of CABG surgery.
- Patients with severe renal and hepatic failure.
- Established congestive heart failure (NYHA II–IV), ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- suffering from alcoholism or currently under ethanol intoxication

4.4 Special Warnings and Precautions for Use Etoricoxib

SUMO-PLUST ablets cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of SUMO-PLUSTablets in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed non-infectious, painful conditions.

The use of SUMO-PLUS Tablets with concomitant systemic NSAIDs, including COX-2 inhibitors, should be avoided, except in patients requiring low-dose acetylsalicylic acid – caution is advised in such patients along with close monitoring. Concomitant use of a systemic NSAID and another systemic NSAID may increase the frequency of gastrointestinal ulcers and bleeding.

CV Effects

CV Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to 3 years' duration have shown an increased risk of serious CV thrombotic events, MI and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimise the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or 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 does increase the risk of serious GI events.

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 MI and stroke

Hypertension

NSAIDs can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including SUMO-PLUSTablets, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Oedema

Fluid retention and oedema have been observed in some patients taking NSAIDs. SUMO-PLUSTablets should be used with caution in patients with fluid retention or heart failure.

GI Effects: Risk of GI Ulceration, Bleeding and Perforation

NSAIDs, including SUMO-PLUSTablets, can cause serious GIadverse 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 GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3–6 months, and in about 2–4% of patients treated for 1 year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or GI bleeding. Patients with a prior history of peptic ulcer disease and/or GI bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared with patients with neither of these risk factors. Other factors that increase the risk for GI 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 GI events are in elderly or debilitated patients and, therefore, special care should be taken in treating this population. To

minimise the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects

Caution should be used when initiating treatment with SUMO-PLUSTablets in patients with considerable dehydration.

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 a NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at the greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and angiotensin-converting enzyme (ACE) inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

Advanced Renal Disease

No information is available from controlled clinical studies regarding the use of SUMO-PLUSTablets in patients with advanced renal disease. Therefore, treatment with SUMO-PLUSTablets is not recommended in these patients with advanced renal disease. If SUMO-PLUSTablets therapy must be initiated, close monitoring of the patient's renal function is advisable.

Hepatic Effects

Elevations of one or more liver tests may occur during therapy with SUMO-PLUSTablets. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations (i.e. less than 3 times the ULN) or greater elevations of transaminases occurred in about 15% of Etoricoxib-treated patients. Of the markers of hepatic function, ALT (SGPT) is recommended for the monitoring of liver injury.

In clinical trials, meaningful elevations (i.e. more than 3 times the ULN) of AST (GOT) (ALT was not measured in all studies) occurred in about 2% of approximately 5,700 patients at some time during Etoricoxib treatment. In a large, open-label, controlled trial of 3,700 patients treated for 2–6 months, patients were monitored first at 8 weeks and 1,200 patients were monitored again at 24 weeks. Meaningful elevations of ALT and/or AST occurred in about 4% of patients and included marked elevations (i.e. more than 8 times

the ULN) in about 1% of the 3,700 patients. In that open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3–8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST was observed in patients receiving Etoricoxib when compared to other NSAIDs. Elevations in transaminases were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis.

Almost all meaningful elevations in transaminases were detected before patients became symptomatic. Abnormal tests occurred during the first 2 months of therapy with Etoricoxib in 42 of the 51 patients in all trials who developed marked transaminase elevations.

In postmarketing reports, cases of drug-induced hepatotoxicity have been reported in the first month and, in some cases, the first 2 months of therapy, but can occur at any time during treatment with Etoricoxib. Postmarketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation.

Physicians should measure transaminases periodically in patients receiving long-term therapy with Etoricoxib, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. Based on clinical trial data and postmarketing experiences, transaminases should be monitored within 4–8 weeks after initiating treatment with Etoricoxib. However, severe hepatic reactions can occur at any time during treatment with Etoricoxib.

If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, abdominal pain, diarrhoea, dark urine, etc.), SUMO-PLUSTablets should be discontinued immediately.

To minimise the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (e.g. nausea, fatigue, lethargy, diarrhoea, pruritus, jaundice, right upper quadrant tenderness, and 'flu-like' symptoms), and the appropriate action patients should take if these signs and symptoms appear.

To minimise the potential risk for an adverse liver related event in patients treated with SUMO-PLUSTablets, the lowest effective dose should be used for the shortest duration possible. Caution should be exercised in prescribing SUMO-PLUSTablets with concomitant drugs that are known to be potentially hepatotoxic (e.g. antibiotics, anti-epileptics).

Anaphylactic Reactions

As with other NSAIDs, anaphylactic reactions may occur both in patients with the aspirin triad and in patients without known sensitivity to NSAIDs or known prior exposure to SUMO-PLUSTablets. It should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. Anaphylaxis-type reactions have been reported with NSAID products, including with Etoricoxib products, such as SUMO-PLUSTablets. Emergency help should be sought in cases where an anaphylactic reaction occurs.

Skin Reactions

NSAIDs, including Etoricoxib, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis, which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Haematological Effects

Anaemia is sometimes seen in patients receiving NSAIDs, including SUMO-PLUSTablets. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including SUMO-PLUSTablets, should have their haemoglobin or haematocrit checked if they exhibit any signs or symptoms of anaemia.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving SUMO-PLUSTablets who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Pre-Existing Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross-reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, SUMO-PLUSTablets should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI

bleeding. In patients on longterm treatment with NSAIDs, including SUMO-PLUSTablets, the CBC and a chemistry profile (including transaminase levels) should be checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, SUMO-PLUSTablets should be discontinued.

Paracetamol

Use in Special

Populations Paediatric

Patients

Not recommended for children under 10 years of age.

Patients with Renal/Hepatic Impairment

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with alcoholic liver disease.

Keep out of the sight and reach of children.

Do not take paracetamol for more than 3 days without consulting a doctor.

Patients should be advised that paracetamol may cause severe skin reactions. If a skin reaction such as reddening, blisters or rash occurs, they should stop its use and seek medical assistance right away.

4.5 Interaction with other medicinal products and other forms of interaction

Etoricoxib

Aspirin: When Etoricoxib is administered with aspirin, its protein-binding is reduced. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of Etoricoxib and aspirin is not generally recommended because of the potential of increased adverse effects.

Methotrexate: NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Cyclosporine: Etoricoxib, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Therefore, concomitant therapy with Etoricoxib may increase cyclosporine's nephrotoxicity. Caution should be used when SUMO-PLUSTablets are

administered concomitantly with cyclosporine.

ACE Inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.

Furosemide: Clinical studies, as well as postmarketing observations, have shown that Etoricoxib 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 NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity. Steady-state plasma lithium and digoxin levels may be increased and ketoconazole levels may be decreased.

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

CYP2C9 Inhibitors or Inducers: Etoricoxib is metabolised by cytochrome (CY) P450 enzymes, predominantly by CYP2C9. Co-administration of Etoricoxib with CYP2C9 inhibitors (e.g. voriconazole) may enhance the exposure and toxicity of Etoricoxib whereas co-administration with CYP2C9 inducers (e.g. rifampin) may lead to compromised efficacy of Etoricoxib. Use caution when dosing Etoricoxib with CYP2C9 inhibitors or inducers; a dosage adjustment may be warranted.

Other Interactions

There is a possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Cases of hypo- and hyperglycaemia have been reported when Etoricoxib was associated with antidiabetic agents.

Concomitant use with other NSAIDs or with corticosteroids may increase the frequency of side effects generally.

NSAIDs can reduce the efficacy of diuretics and other antihypertensive drugs, including ACE inhibitors, angiotensin II antagonists (AIIA) and beta-blockers.

In patients with impaired renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of an ACE

inhibitor or an AIIA and/or diuretics with a cyclo-oxygenase inhibitor can increase the deterioration of the renal function, including the possibility of acute renal failure, which is usually reversible.

Antacids may delay the absorption of Etoricoxib. Magnesium-containing antacids have been shown to exacerbate misoprostol-associated diarrhoea.

Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

NSAIDs should not be used for 8–12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Voriconazole increased C_{max} and AUC of Etoricoxib (50 mg single dose) by 114% and 78%, respectively.

Paracetamol

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone. However, concurrent use need not be avoided.

The speed of absorption of paracetamol is reduced by colestyramine. Therefore, colestyramine should not be taken within 1 hour if maximal analgesia is required.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

Restriction or avoidance of concomitant regular paracetamol use should be followed with imatinib.

Chloramphenicol plasma concentration is increased when given with paracetamol.

4.6 Fertility, pregnancy and lactation

Pregnant Women

Etoricoxib

Teratogenic Effects: Pregnancy Category C

Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.

Non-Teratogenic Effects: Because of the known effects of NSAIDs on the foetal CV system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided**.**

Paracetamol

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of their doctor regarding its use.

A large amount of data on pregnant women indicate neither malformative, nor foeto-/neonatal toxicity. Paracetamol can be used during pregnancy if clinically needed; however, it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

In late pregnancy, as with other NSAIDs, SUMO-PLUSTablets should be avoided because they may cause premature closure of the ductus arteriosus.

Labour and Delivery

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. The effects of Etoricoxib on labour and delivery in pregnant women are unknown.

Lactating Women

It is not known whether Etoricoxib is excreted in human milk. Paracetamol is excreted in breast milk but not in clinically significant amount. Available published data do not contraindicate breastfeeding.

Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SUMO-PLUSTablets, 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.

Paediatric Patients

Safety and effectiveness in paediatric patients have not been established.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness, vertigo or somnolence while taking etoricoxib should refrain from driving or operating machinery.

4.8 *Undesirable effects*

Etoricoxib

In patients taking Etoricoxib, or other NSAIDs, the most frequently reported adverse experiences occurring in approximately 1–10% of patients are as follows:

GI Events: These include abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, GI ulcers (gastric/duodenal) and vomiting.

Other: Abnormal renal function, anaemia, dizziness, oedema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes and tinnitus.

Additional adverse experiences reported occasionally include the following:

Body as a Whole: **fever, infection, sepsis**

CV System: congestive heart failure, hypertension, tachycardia, syncope

Digestive System: dry mouth, oesophagitis, gastric/peptic ulcers, gastritis, GI bleeding, glossitis, haematemesis, hepatitis, jaundice

Haemic and Lymphatic System: ecchymosis, eosinophilia, leucopaenia, melaena, purpura, rectal bleeding, stomatitis, thrombocytopaenia

Metabolic and Nutritional: weight changes
Nervous System: anxiety, asthenia, confusion, depression, dream

abnormalities, drowsiness, insomnia, malaise, nervousness, paraesthesia,

somnolence, tremors, vertigo ***Respiratory System****:* asthma, dyspnoea

Skin and Appendages: alopecia, photosensitivity, sweating increased

Special Senses: blurred vision

Urogenital System: cystitis, dysuria, haematuria, interstitial nephritis, oliguria/polyuria, proteinuria, renal failure

Other adverse reactions, which occur rarely, are as follows:

Body as a Whole: anaphylactic reactions, appetite changes, death

CV System: arrhythmia, hypotension, myocardial infarction, palpitations, vasculitis

Digestive System: colitis, eructation, fulminant hepatitis with and without jaundice, liver failure, liver necrosis, pancreatitis.

Haemic and Lymphatic System: agranulocytosis, haemolytic anaemia, aplastic anaemia, lymphadenopathy, pancytopaenia

Metabolic and Nutritional: hyperglycaemia

Nervous System: convulsions, coma, hallucinations, meningitis

Respiratory System: respiratory depression, pneumonia

Skin and Appendages: angio-oedema, toxic epidermal necrolysis,

erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, urticaria

Special Senses: conjunctivitis, hearing impairment.

Nicolau's syndrome, also known as livedo-like dermatitis or embolia cutis medicamentosa, is a rare complication reported following intramuscular Etoricoxib injection.

Paracetamol

The information below lists reported adverse reactions, ranked using the following frequency classification: 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).

Immune System Disorders

Hypersensitivity, including skin rash, may occur

Not Known: anaphylactic shock, angio-oedema

Blood and Lymphatic System Disorders

Not Known: blood dyscrasias, including thrombocytopaenia and agranulocytosis

Skin and Subcutaneous Disorders

Very rare cases of serious skin reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis, and fixed drug eruption have been reported.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important as it allows continued monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the marketing authorisation holder or, where applicable, via the national reporting system.

4.9 Overdose

Etoricoxib

Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, confusion, disorientation, excitation, coma, tinnitus, fainting or convulsions, vomiting, headache, dizziness and epigastric pain, which are generally reversible with supportive care. GI complaints, including GI 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. In the case of significant poisoning, acute renal failure and liver damage are possible.

Patients should be managed by symptomatic and supportive care following a NSAID overdose. There are no specific antidotes. Emesis and/or activated charcoal (60–100 g in adults, 1–2 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 (5–10 times the usual dose). Forced diuresis, alkalinisation of urine, haemodialysis or haemoperfusion may not be useful due to high protein-binding.

Management of acute poisoning with NSAIDs essentially consists of supportive and symptomatic measures. It is reasonable to take measures to reduce absorption of any recently consumed drug by forced emesis, gastric lavage or activated charcoal. Induced diuresis may be beneficial because Etoricoxib and misoprostol metabolites are excreted in the urine, provided that the patient does not develop renal failure at Etoricoxib overdose. Special measures such as haemodialysis or haemoperfusion are probably unlikely to be helpful in accelerating the elimination of Etoricoxib, due to the high protein binding and extensive metabolism.

Paracetamol

Liver damage is possible in adults who have taken 10 g or more of paracetamol. Ingestion of 5 g or more of paracetamol may lead to liver damage if the patient has risk factors**.**

5. Pharmacological properties

5.1 Pharmacodynamic properties

SUMO-PLUS Tablets contain Etoricoxib,paracetamol. Etoricoxib is a NSAID (non-steroidal anti-inflammatory drug) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of Etoricoxib, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition. Paracetamol has analgesic and antipyretic actions.

Etoricoxib

Pharmacotherapeutic group (ATC code): M01AB55

Etoricoxib is a NSAID that has been shown to have anti-inflammatory and analgesic properties and is effective in treating the signs and symptoms of arthritic conditions.

Paracetamol

ATC code: N02B E01, Other analgesics and antipyretics

Analgesic: The mechanism of analgesic action has not been fully determined. Paracetamol may act predominately by inhibiting prostaglandin synthesis in the central nervous system and, to a lesser extent, through a peripheral action by blocking pain-impulse generation.

The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation.

Antipyretic: Paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat-regulation centre to produce peripheral vasodilation, resulting in increased blood flow through the skin, sweating and heat loss. The central action probably involves inhibition of prostaglandin synthesis in the hypothalamus. The drug has no effect on the CV and respiratory systems and unlike salicylates, it does not cause gastric irritation or bleeding.

Paracetamol has analgesic and antipyretic actions but it has no useful anti-inflammatory properties.

5.2 Pharmacokinetic properties

Etoricoxib

Absorption

Etoricoxib is 100% absorbed after oral administration compared to intravenous (IV) administration as measured by urine recovery. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available. Food has no significant effect on the extent of Etoricoxib absorption. However, there is usually a delay in the onset of absorption of 1–4.5 hours and a reduction in peak plasma levels of <20%.

Distribution

The apparent volume of distribution (V/F) of Etoricoxib is 1.4 L/kg.

Etoricoxib is more than 99% bound to human serum proteins, primarily to albumin. Serum protein-binding is constant over the concentration range (0.15–105 µg/mL) achieved with recommended doses.

Etoricoxib diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of Etoricoxib.

Metabolism

Five Etoricoxib metabolites have been identified in human plasma and urine. The metabolites include 4'-hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3' hydroxy-4'-methoxy-Etoricoxib. The major Etoricoxib metabolite, 4'-hydroxy-Etoricoxib, has very weak pharmacologic activity. The formation of 4'-hydroxy- Etoricoxib is primarily mediated by CPY2C9. Both Etoricoxib and its oxidative metabolites undergo glucuronidation or sulphation followed by biliary excretion. Acylglucuronidation mediated by UGT2B7 and oxidation mediated by CPY2C8 may also play a role in Etoricoxib metabolism. CYP3A4 is responsible for the formation of minor metabolites, 5-hydroxyand 3'-hydroxy-Etoricoxib. In patients with renal dysfunction, peak concentrations of the metabolites, 4'-hydroxy- and 5-hydroxy-Etoricoxib, were approximately 50% and 4% of the parent compound after single oral dosing compared with 27% and 1%, respectively, in normal healthy subjects**.**

Excretion

Etoricoxib is eliminated through metabolism and subsequent urinary and biliary

excretion of the glucuronide and the sulphate conjugates of the metabolites. Little or no free unchanged Etoricoxib is excreted in the urine. Approximately 65% of the dose is excreted in the urine and approximately 35% in the bile as conjugates of unchanged Etoricoxib plus metabolites. Because renal elimination is not a significant pathway of elimination for unchanged Etoricoxib, dosing adjustment in patients with mild-to-moderate renal dysfunction is not necessary. The terminal half-life of unchanged Etoricoxib is approximately 2 hours.

Paracetamol

Paracetamol is readily absorbed from the GI tract, with peak plasma levels occurring about 30 minutes to 2 hours after ingestion.

It is metabolised in the liver (90–95%) and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted unchanged.

The elimination half-life of paracetamol varies from about 1 to 4 hours. Plasma protein-binding is negligible at usual therapeutic doses but increases with increasing concentrations.

A minor hydroxylated metabolite (N-acetyl-p-benzoquinoneimine), which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione, may accumulate following paracetamol overdosage and cause liver damage.

The time to peak plasma concentration of paracetamol is 0.5–2 hours, the

time to peak effect 1–3 hours, and the duration of action is 3–4 hours.

Non-Clinical Properties

Animal Toxicology or Pharmacology

5.3 Preclinical safety data

In preclinical studies, etoricoxib has been demonstrated not to be genotoxic. Etoricoxib was not carcinogenic in mice. Rats developed hepatocellular and thyroid follicular cell adenomas at > 2-times the daily human dose [90 mg] based on systemic exposure when dosed daily for approximately two years. Hepatocellular and thyroid follicular cell adenomas observed in rats are considered to be a consequence of rat-specific mechanism related to hepatic CYP enzyme induction. Etoricoxib has not been shown to cause hepatic CYP3A enzyme induction in humans.

In the rat, gastrointestinal toxicity of etoricoxib increased with dose and exposure time. In the 14-week toxicity study etoricoxib caused gastrointestinal ulcers at exposures greater than those seen in man at the therapeutic dose. In the 53- and 106-week toxicity study, gastrointestinal ulcers were also seen at exposures comparable to those seen in man at the therapeutic dose. In dogs, renal and gastrointestinal abnormalities were seen at high exposures.

Etoricoxib was not teratogenic in reproductive toxicity studies conducted in rats at 15 mg/kg/day (this represents approximately 1.5 times the daily human dose [90 mg] based on systemic exposure). In rabbits, a treatment related increase in cardiovascular malformations was observed at exposure levels below the clinical exposure at the daily human dose (90mg). However no treatment-related external or skeletal foetal malformations were observed. In rats and rabbits, there was a dose dependent increase in post implantation loss at exposures greater than or equal to 1.5 times the human exposure (see sections 4.3 and 4.6).

Etoricoxib is excreted in the milk of lactating rats at concentrations approximately two-fold those in plasma. There was a decrease in pup body weight following exposure of pups to milk from dams administered etoricoxib during lactation.

6. Pharmaceutical particulars

6.1 List of

excipients Cross

carmellose Sodium

Colloidal silicon

dioxide Sodium

Lauryl Sulphate

Microcrystalline

Cellulose Color

Titanium Dioxide

Starch

Povidone K-30

Magnesium

Stearate Talcum

Sodium Starch Glycollate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

No special storage precautions

6.5 Nature and contents of container

10x1x10 Alu Alu Pack

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing authorisation holder

Javia International Limited

8. Marketing authorisation number(s)

H2025/CTD11764/22237

9. Date of first authorisation/renewal of the authorization

12th June 2025

10. Date of revision of the text

12th June 2025