ATTACHMENT 1

Arial (bold) = 18pt

Torixib®
Film Coated Tablet 60mg
Film Coated Tablet 90mg
Film Coated Tablet 120mg

Arial = 6pt

Active Ingredient:
Each film coated tablet contains:
Etoricoxib..... 60mg
Etoricoxib..... 90mg
Etoricoxib..... 120mg

Pharmacotherapeutic Group:
Anti-inflammatory and antirheumatic products, non-steroids, coxibs, ATC code: M01AH05

Pharmacodynamics
Mechanism of action
Etoricoxib is an oral, selective cyclo-oxygenase-2 (COX-2) inhibitor within the clinical dose range.

Etoricoxib produced dose-dependent inhibition of COX-2 without inhibition of COX-1 at doses up to 150mg daily. Etoricoxib did not inhibit gastric prostaglandin synthesis and had no effect on platelet function. Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.

Pharmacokinetics
Absorption
The onset of action of etoricoxib occurred as early as 24 minutes after dosing. Orally administered etoricoxib is well absorbed. The mean oral bioavailability is approximately 100%. Following 120mg once-daily dosing to steady state, the peak plasma concentration (geometric mean C_{max} = 3.6mcg/mL) was observed at approximately 1 hour (T_{max}) after administration to fasted adults. The geometric mean $AUC_{0\text{-}24hr}$ was 37.8mcg•hr/mL. The pharmacokinetics of etoricoxib are linear across the clinical dose range. A standard meal had no clinically meaningful effect on the extent or rate of absorption of a dose of etoricoxib 120mg. In clinical trials, etoricoxib was administered without regard to food.
Distribution
Etoricoxib is approximately 92% bound to human plasma protein over the range of concentrations of 0.05 to 5mcg/mL. The volume of distribution at steady state (V_{dss}) is approximately 120L in humans. Etoricoxib crosses the placenta in rats and rabbits, and the blood-brain barrier in rats.
Metabolism
Etoricoxib is extensively metabolised with <1% of a dose recovered in urine as the parent drug. The major route of metabolism to form the 6'-hydroxymethyl derivative is catalysed by cytochrome P450 (CYP) enzymes.
Five metabolites have been identified in man. The principal metabolite is the 6'-carboxylic acid derivative of etoricoxib formed by further oxidation of the 6'-hydroxymethyl derivative. These principal metabolites either demonstrate no measurable activity or are only weakly active as COX-2 inhibitors. None of these metabolites inhibit COX-1.
Elimination
Elimination of etoricoxib occurs almost exclusively through metabolism followed by renal excretion. Steady state concentrations of etoricoxib are reached within seven days of once-daily administration of 120mg, with an accumulation ratio of approximately 2, corresponding to an accumulation half-life of approximately 22 hours. The plasma clearance is estimated to be approximately 50mL/min.

Special Populations:
Use in paediatric
Safety and effectiveness of etoricoxib in paediatric patients have not been established.
Use in the elderly
Pharmacokinetics in the elderly (65 years of age and older) are similar to those in the young.

Indication(s):
TORIXIB® is indicated for:
- Acute and chronic treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA)
- Treatment of ankylosing spondylitis (AS)
- Treatment of acute gouty arthritis
- Treatment of acute pain, including that related to primary dysmenorrhoea and minor dental procedures.
- Chronic low back pain (60 mg only)

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks.

Dosage and Administration(s):
TORIXIB® should be administered for the shortest duration possible and the lowest effective daily dose should be used.
TORIXIB® consists of 60, 90 & 120mg tablets. TORIXIB® tablet is not able to deliver all approved dose regimens of etoricoxib. Therefore, other approved dosage forms and strengths of etoricoxib should be used in such cases.

Osteoarthritis
The recommended dose is 30mg or 60mg once daily.

Rheumatoid Arthritis
The recommended dose is 60 mg or 90 mg once daily. The minimum effective daily dose is 60 mg once daily. In some patients, 90 mg once daily may provide increased therapeutic benefit.

Ankylosing Spondylitis
The recommended dose is 60 mg or 90 mg once daily. The minimum effective daily dose is 60 mg once daily. In some patients, 90 mg once daily may provide increased therapeutic benefit.

Chronic Low Back Pain
The recommended dose is 60 mg once daily.

Acute Pain
In the following acute painful conditions, TORIXIB® should be used only for the acute symptomatic period, limited to a maximum of 8 days treatment:
- *Acute Gouty Arthritis*
  The recommended dose is 120 mg once daily.
- *Primary Dysmenorrhea*
  The recommended dose is 120 mg once daily.
- *Minor Dental Procedures*
  The recommended dose is 90 mg once daily.

Doses greater than those recommended for each indication have either not demonstrated additional efficacy or have not been studied. Therefore:

The dose for OA should not exceed 60 mg daily.
The dose for RA should not exceed 90 mg daily.
The dose for ankylosing spondylitis should not exceed 90 mg daily.
The dose for acute gout should not exceed 120 mg daily.
The dose for acute pain and primary dysmenorrhea should not exceed 120 mg daily.
The dose of chronic low back pain should not exceed 60 mg daily.
The dose for minor dental procedures should not exceed 90 mg daily.

Given the association between cardiovascular risk and exposure to COX-2 Inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment the patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

Elderly, Gender, Race
No dosage adjustment in TORIXIB® is necessary for the elderly or based on gender or race.

Hepatic Insufficiency
In patients with mild hepatic insufficiency (Child-Pugh score 5-6), a dose of 60mg once daily should not be exceeded. In patients with moderate hepatic insufficiency (Child-Pugh score 7- 9), the dose should be reduced; a dose of 60mg every other day should not be exceeded, administration of 30mg once daily can also be considered. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9).

Renal Insufficiency
In patients with advanced renal disease (creatinine clearance <30mL/min), treatment with TORIXIB® is not recommended. No dosage adjustment is necessary for patients with lesser degrees of renal insufficiency (creatinine clearance ≥30mL/min).

Route of Administration(s):
TORIXIB® is administered orally. TORIXIB® may be taken with or without food.

Contraindication(s):
Etoricoxib is contraindicated in patients with:
- Hypersensitivity to any component of this product.
- Congestive heart failure (NYHA II-IV).
- Increased risk of cardiovascular disease (ischeamic heart disease and stroke).
- Established ischeamic heart disease, peripheral arterial disease and/or cerebrovascular disease (including patients who have recently undergone coronary artery bypass graft surgery or angioplasty).
- Hypertension (high blood pressure) whose blood pressure is not under control.
- Patients with active peptic ulceration or gastrointestinal (GI) bleeding.
- Patients with severe hepatic dysfunction (Child-Pugh score >9).
- Patients with estimated creatinine clearance <30 ml/min.
- Patients who have developed signs of bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria following the administration of acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs).
- Pregnancy and lactation.
- Children and adolescents under 16 years of age.
- Patients with inflammatory bowel disease.

Warning and Precaution(s):
As the cardiovascular risks of selective COX-2 inhibitors may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

Patients with significant risk factors for cardiovascular events (e.g. patients with risk factors of heart disease, hypertension, hyperlipidaemia, diabetes mellitus, smoking patients and patients with peripheral arterial disease) should only be treated with etoricoxib after careful consideration.

Selective COX-2 inhibitors are not a substitute for aspirin for cardiovascular prophylaxis because of their lack of effect on platelets. Because etoricoxib, a member of this class, does not inhibit platelet aggregation, antiplatelet therapies should not be discontinued.

There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) for etoricoxib, other selective COX-2 inhibitors and NSAIDs, when taken concomitantly with acetylsalicylic acid (even at low doses).

In patients with advanced renal disease, treatment with etoricoxib is not recommended. Clinical experience in patients with estimated creatinine clearance of <30mL/min is very limited. If therapy with etoricoxib must be initiated in such patients, close monitoring of the patient's renal function is advisable.

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion. Therefore, under conditions of compromised renal perfusion, administration of etoricoxib may cause a reduction in prostaglandin formation and, secondarily, in renal blood flow, and thereby impair renal function. Patients at greatest risk of this response are those with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. Monitoring of renal function in such patients should be considered.

Caution should be used when initiating treatment with etoricoxib in patients with considerable dehydration. It is advisable to rehydrate patients prior to starting therapy with etoricoxib.

L
260mm
±
2mm

W
220mm ± 2mm

ATTACHMENT 2

Item Code	: 204XXX draft 05 Jan 2024
PM Code	: Ins.P TXT, TXT6, TXT9
Measurement(mm) ± 2mm	: 260(L) x 220(W)
CURSOR (ATTACHMENT 1)	:
CURSOR (ATTACHMENT 2)	:
Colour of Artwork	: K 100
Source of Artwork	: MAC 1 / CC

ATTACHMENT 3

As with other drugs known to inhibit prostaglandin synthesis, fluid retention, edema and hypertension have been observed in some patients taking etoricoxib. The possibility of fluid retention, edema or hypertension should be taken into consideration when etoricoxib is used in patients with pre-existing edema, hypertension, or heart failure. All nonsteroidal anti-inflammatory drugs (NSAIDs), including etoricoxib, can be associated with new onset or recurrent congestive heart failure. Etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses. Therefore, special attention should be paid to blood pressure monitoring during treatment with etoricoxib. If blood pressure rises significantly, alternative treatment should be considered.
Physicians should be aware that individual patients may develop upper gastrointestinal (GI) ulcers/ulcer complications irrespective of treatment. Upper GI ulcers/ulcer complications have occurred in patients treated with etoricoxib. These events can occur at any time during use and without warning symptoms. Independent of treatment, patients with a prior history of GI perforation, ulcers and bleeding (PUB) and patients greater than 65 years of age are known to be at a higher risk for a PUB.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (three times the upper limit of normal) are detected, etoricoxib should be discontinued.

Etoricoxib should be used with caution in patients who have previously experienced acute asthmatic attacks, urticaria, or rhinitis, which were precipitated by salicylates or non-selective cyclooxygenase inhibitors. Since the pathophysiology of these reactions is unknown, physicians should weigh the potential benefits of prescribing etoricoxib versus the potential risks.

When using etoricoxib in the elderly and in patients with renal, hepatic, or cardiac dysfunction, medically appropriate supervision should be maintained. If these patients deteriorate during treatment, appropriate measures should be taken, including discontinuation of therapy.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs and some selective COX-2 inhibitors during post-marketing surveillance. These serious events may occur without warning. Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving etoricoxib. Some selective COX-2 inhibitors have been associated with an increased risk of skin reactions in patients with a history of any drug allergy. Etoricoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Etoricoxib may mask fever, which is a sign of infection. The physician should be aware of this when using etoricoxib in patients being treated for infection.

Risk of GI Ulceration, Bleeding and Perforation with NSAIDs
Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAIDs therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious adverse events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

The use of etoricoxib, as with any medicinal product known to inhibit cyclooxygenase / prostaglandin synthesis, is not recommended in women attempting to conceive.

Interaction with Other Medicaments(s):
Warfarin
The administration of etoricoxib 120mg daily was associated with an approximate 13% increase in prothrombin time International Normalized Ratio (INR). Standard monitoring of INR values should be conducted when therapy with etoricoxib is initiated or changed, particularly in the first few days, in patients receiving warfarin or similar agents.

Rifampin
Co-administration of etoricoxib with rifampin, a potent inducer of hepatic metabolism, produced a 65% decrease in etoricoxib plasma area under the curve (AUC). This interaction should be considered when etoricoxib is co-administered with rifampin.

Methotrexate
Monitoring for methotrexate-related toxicity should be considered when etoricoxib at doses greater than 90mg daily and methotrexate are administered concomitantly.

Diuretics, Angiotensin Converting Enzyme (ACE) Inhibitors and Angiotensin II Antagonists (AIIAs)
Selective COX-2 inhibitors may diminish the antihypertensive effect of diuretics, ACE inhibitors and AIIAs. This interaction should be given consideration in patients taking etoricoxib concomitantly with these products.

In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with NSAIDs, including selective COX-2 inhibitors, the co-administration of ACE inhibitors or AIIAs may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution, especially in the elderly.

Lithium
Non-selective NSAIDs and selective COX-2 inhibitors may increase plasma lithium levels. This interaction should be given consideration in patients taking etoricoxib concomitantly with lithium.

Aspirin
Etoricoxib can be used concomitantly with low-dose aspirin at doses for cardiovascular prophylaxis. At steady state, etoricoxib 120mg once daily had no effect on the anti-platelet activity of low-dose aspirin (81mg once daily). However, concomitant administration of low-dose aspirin with etoricoxib increases the rate of GI ulceration or other complications compared to use of etoricoxib alone.

ATTACHMENT 4

Oral Contraceptives
An increase in ethinyl estradiol (EE) concentration should be considered when selecting an appropriate oral contraceptive for use with etoricoxib. An increase in EE exposure can increase the incidence of adverse events associated with oral contraceptives (e.g., venous thrombo-embolic events in women at risk).

Hormone Replacement Therapy
The increases in estrogenic concentration should be taken into consideration when selecting post-menopausal hormone therapy for use with etoricoxib.

Other
Etoricoxib did not have clinically important effects on the pharmacokinetics of prednisone/prednisolone or digoxin.
Antacids and ketoconazole (a potent inhibitor of CYP3A4) did not have clinically important effects on the pharmacokinetics of etoricoxib.

Pregnancy and Lactation(s):
The use of etoricoxib, as with any drug substance known to inhibit COX-2, is not recommended in women attempting to conceive. No clinical data on exposed pregnancies are available for etoricoxib. Studies in animals have shown reproductive toxicity. The potential for human risk in pregnancy is unknown. Etoricoxib, as with other medicinal products inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester. Etoricoxib is contraindicated in pregnancy. If a woman becomes pregnant during treatment, etoricoxib should be discontinued.
Etoricoxib is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the possible adverse effects of drugs that inhibit prostaglandin synthesis on nursing infants, 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.

Side Effect(s):
Blood and lymphatic system disorders: thrombocytopenia.
Immune system disorders: hypersensitivity reactions, anaphylactic/anaphylactoid reactions including shock.
Metabolism and nutrition disorders: hyperkalemia.
Psychiatric disorders: anxiety, insomnia, confusion, hallucinations, depression, restlessness.
Nervous system disorders: dysgeusia, somnolence.
Eye disorders: blurred vision.
Cardiac disorders: congestive heart failure, palpitations, angina, arrhythmia.
Vascular disorders: hypertensive crisis.
Respiratory, thoracic and mediastinal disorders: bronchospasm.
Gastrointestinal disorders: abdominal pain, oral ulcers, peptic ulcers including perforation and bleeding (mainly in elderly patients), vomiting, diarrhoea.
Hepatobiliary disorders: hepatitis, jaundice, hepatic failure.
Skin and subcutaneous tissue disorders: angioedema, pruritus, erythema, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, fixed drug eruption.
Renal and urinary disorders: renal insufficiency, including renal failure.

Effects on Ability to Drive and Use Machine:
Etoricoxib may cause dizziness, vertigo or somnolence. If affected, do not drive or operate machinery.

Symptoms and Treatment of Overdose(s):
The most frequently observed adverse experience were consistent with the safety profile for etoricoxib (e.g. gastrointestinal events, renovascular events). In the event of overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.
Etoricoxib is not dialyzable by hemodialysis; it is not known whether etoricoxib is dialyzable by peritoneal dialysis.

Storage Condition(s):
Store below 30°C. Protect from moisture and light.

Shelf Life(s):
3 years from the date of manufacture.

Product Description and Packing(s)
TORIXIB® FILM COATED TABLET 60mg:
A dark green round film coated tablet.
Alu-alu blister packing of 10's x 10

TORIXIB® FILM COATED TABLET 90mg:
A white round film coated tablet, one side impressed with "Y".
Alu-alu blister packing of 10's x 10

TORIXIB® FILM COATED TABLET 120mg:
A light green round film coated tablet.
Alu-alu blister packing of 10's x 10

Manufacturer and Product Registration Holder:
Y.S.P. INDUSTRIES (M) SDN. BHD. (199001001034)
Lot 3, 5, 7 & 12, Jalan P/7, Section 13,
Kawasan Perindustrian Bandar Baru Bangi,
43000 Kajang, Selangor, Malaysia.
Ordering Line: 1 800 88 3027
Product Info: 1 800 88 3679

xxxxxx printing code xxxxxx

Date of revision: 05 Jan 2024

Item Code	: 204XXX draft 05 Jan 2024
PM Code	: Ins.P TXT, TXT6, TXT9
Measurement(mm) ± 2mm	: 260(L) x 220(W)
CURSOR (ATTACHMENT 1)	:
CURSOR (ATTACHMENT 2)	:
Colour of Artwork	: K 100
Source of Artwork	: MAC 1 / CC

L
260mm
±
2mm

W
220mm ± 2mm