Professional Information

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ETORICOXIB 60 BIOTECH, 60 mg etoricoxib film-coated tablets

ETORICOXIB 90 BIOTECH, 90 mg etoricoxib film-coated tablets

ETORICOXIB 120 BIOTECH, 120 mg etoricoxib film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ETORICOXIB 60 BIOTECH: Each film-coated tablet contains 60 mg of etoricoxib.

ETORICOXIB 90 BIOTECH: Each film-coated tablet contains 90 mg of etoricoxib.

ETORICOXIB 120 BIOTECH: Each film-coated tablet contains 120 mg of etoricoxib.

Contains sugar (lactose monohydrate): 1,68 mg per 60 mg tablet; 2,52 mg per 90 mg tablet and 3,36 mg per 120 mg tablet.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

Etoricoxib Tablets 60 mg: Green, round, biconvex, film-coated tablets debossed with ‘444’ on one side and ‘L’ on other side.

Etoricoxib Tablets 90 mg: White to off-white, round, biconvex, film-coated tablets debossed with '445' on one side and 'L' on other side.

Etoricoxib Tablets 120 mg: Pale-green, round, biconvex, film-coated tablets debossed with '446' on one side and 'L' on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ETORICOXIB BIOTECH is indicated tor:

- symptomatic relief of rheumatoid arthritis (RA)
- treatment of ankylosing spondylitis (AS)
- treatment of acute gouty arthritis
- short term relief of acute pain, treatment limited to a maximum period of 8 days
- treatment of primary dysmenorrhoea
- treatment of moderate to severe acute post-operative pain associated with dental surgery.

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks (see section 4.4).

4.2 Posology and method of administration

Posology

ETORICOXIB BIOTECH may be taken with or without food.

Use the lowest effective dose for the shortest possible duration of time.

Rheumatoid Arthritis (RA)

The recommended dose is 90 mg once daily. In some patients, the 60 mg once daily dose may provide adequate

therapeutic benefit.

The dose for rheumatoid arthritis should not exceed 90 mg daily.

Ankylosing Spondylitis

The recommended dose is 90 mg once daily.

The dose for ankylosing spondylitis should not exceed 90 mg daily.

Short term relief of acute pain

The recommended dose is 90 mg or 120 mg once daily, limited to a maximum of 8 days treatment. The dose for acute pain should not exceed 120 mg daily.

Acute Gouty Arthritis

The recommended dose is 120 mg once daily.

ETORICOXIB BIOTECH 120 mg should be used only for the acute symptomatic period, limited to a maximum of 8 days treatment.

The dose for acute gout should not exceed 120 mg daily.

Primary Dysmenorrhoea

The recommended dose is 120 mg once daily. The dose for primary dysmenorrhoea should not exceed 120 mg daily.

Post-operative Dental Pain

The recommended dose is 90 mg once daily. The dose for post-operative dental surgery pain should not exceed 90 mg daily.

Higher doses than those recommended for each indication have either not demonstrated additional efficacy or have not been studied.

Therefore, the dose for each indication is the maximum recommended dose.

As the cardiovascular risks of selective COX-2 inhibitors, such as ETORICOXIB BIOTECH, 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 (see section 4.4).

Elderly

No dosage adjustment in ETORICOXIB BIOTECH is necessary for the elderly,-although the elderly may be more susceptible to renal, gastrointestinal and cardiovascular side effects (see sections 4.4 and 4.8).

When using ETORICOXIB BIOTECH in the elderly and in patients with renal, hepatic or cardiac dysfunction, medically appropriate supervision should be intensified. If patients show deterioration during treatment, appropriate measures should be taken, including discontinuation of ETORICOXIB BIOTECH.

Hepatic Insufficiency

In patients with mild hepatic insufficiency (Child-Pugh score 5 to 6), a dose of 60 mg once daily should not be exceeded.

In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), the dose should be reduced; a dose of 60 mg *every other day* should not be exceeded.

There is limited clinical experience particularly in patients with moderate hepatic dysfunction and caution is advised.

There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score greater than 9), therefore its use is contraindicated in these patients (see section 4.3).

Renal Insufficiency

No dosage adjustment is necessary for patients with lesser degrees of renal insufficiency (creatinine clearance greater than or equal to 30 ml/min).

The use of ETORICOXIB BIOTECH in patients with creatinine clearance less than 30 ml/min is contraindicated (see section 4.3).

Method of administration

ETORICOXIB BIOTECH must be taken orally.

4.3 Contraindications

ETORICOXIB BIOTECH is contraindicated in the following conditions:

Patients with known hypersensitivity to etoricoxib to any of the excipients of ETORICOXIB BIOTECH.

Patients with active peptic ulceration or gastrointestinal (GI) bleeding.

Patients with severe hepatic dysfunction (Child-Pugh score greater than 9 or serum albumin less than 25 g/l).

Patients with estimated creatinine clearance less than 30 ml/min.

Patients who have developed signs of asthma, acute rhinitis, nasal polyps, angioedema or urticaria following the administration of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) including COX-2 inhibitors. (See section 4.4)

Hypertension which has not been adequately controlled.

Pregnancy and lactation.

Children and adolescents under 16 years of age.

Patients with inflammatory bowel disease.

Patients with congestive heart failure (NYHA II – IV)

Established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease.

Perioperative analgesia in the setting of coronary artery bypass surgery (CABG).

Lithium therapy

Concomitant administration with ETORICOXIB BIOTECH may lead to toxic blood concentrations of lithium (see section 4.5).

Digoxin

There was an approximate increase of 33 % in the digoxin C_{max} in healthy volunteers (see section 4.5).

4.4 Special warnings and precautions for use

ETORICOXIB BIOTECH may predispose to cardiovascular events, gastrointestinal events or cutaneous reactions which may be fatal.

Clinical trials suggest that the selective COX-2 inhibitor class of medicines, such as ETORICOXIB BIOTECH, are associated with an increased risk of arterial thrombotic events (especially myocardial infarction (MI) and stroke).

Renal effects

Long-term use of NSAIDs such as ETORICOXIB BIOTECH has led to renal papillary necrosis and other renal injury.

Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion.

Therefore, administration of ETORICOXIB BIOTECH under conditions of compromised renal perfusion may result in a reduction in prostaglandin formation and secondarily, in renal blood flow thereby impairing renal function.

The risk of this response is greatest in patients with pre-existing significantly impaired renal function, uncompensated heart failure or cirrhosis.

Monitoring of renal and hepatic function in such patients should be considered.

Dehydration

ETORICOXIB BIOTECH should be used with caution when initiating treatment in patients with dehydration.

The rehydration of patients is recommended before starting therapy with ETORICOXIB BIOTECH.

Fluid retention, oedema and hypertension

Due to inhibition of prostaglandin synthesis, fluid retention, oedema and hypertension have been reported in patients taking ETORICOXIB BIOTECH. ETORICOXIB BIOTECH should therefore be used with caution in patients with compromised cardiac function and other conditions predisposing to or worsened by fluid retention.

Patients with pre-existing congestive heart failure or hypertension should be closely monitored.

All Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), including ETORICOXIB BIOTECH, can be associated with new onset or recurrent congestive heart failure.

ETORICOXIB BIOTECH should be used with caution in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and in patients with pre-existing oedema from any other reason.

Appropriate measures including cessation of ETORICOXIB BIOTECH should be taken in the event of evidence of worsening in the condition of these patients.

ETORICOXIB BIOTECH may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, especially at high doses.

Special attention should therefore be given to blood pressure monitoring during treatment with ETORICOXIB BIOTECH.

Alternative treatment should be considered if significant increase in blood pressure occurs.

Cardiovascular effects

The selective COX-2 inhibitor class of medicines such as ETORICOXIB BIOTECH may be associated with an increased risk of thrombotic events (especially myocardial infarction and stroke), relative to placebo and some

NSAIDs.

There appears to be a higher risk for cardiovascular events with higher doses and longer duration of treatment therefore the shortest duration possible and the lowest effective daily dose should be used.

The need of the patient for symptomatic relief and the patient response to therapy should be re-evaluated periodically.

Caution is advised when ETORICOXIB BIOTECH is prescribed to patients with cardiovascular risk factors e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking.

ETORICOXIB BIOTECH is not a substitute for aspirin for cardiovascular prophylaxis because of its lack of effect on platelets.

Antiplatelet therapies should not be discontinued, as ETORICOXIB BIOTECH does not inhibit platelet aggregation, and if indicated should be considered in patients at risk for or with a history of cardiovascular or other thrombotic events.

There is no consistent evidence that concomitant use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with ETORICOXIB BIOTECH (see section 4.5).

Skin reactions

Serious skin reactions, which may be fatal, may occur. Cases of exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported less frequently in association with the use of NSAIDs and some selective COX-2 inhibitors such as ETORICOXIB BIOTECH, during post-marketing surveillance (see section 4.8). These serious events may occur without warning.

As the onset of the reaction occur in the majority of cases within the first month of treatment, patients appear to be at highest risk for these reactions early in the course of therapy.

There have been reports of serious hypersensitivity reactions (such as anaphylaxis and angioedema) in patients receiving ETORICOXIB BIOTECH (see section 4.8).

Patients with a history of any medicine allergy have been associated with an increased risk of skin reactions with

the use of some selective COX-2 inhibitors such as ETORICOXIB BIOTECH.

The use of ETORICOXIB BIOTECH should be stopped at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as ETORICOXIB BIOTECH. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophillia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue ETORICOXIB BIOTECH and evaluate the patient immediately.

Gastrointestinal effects

Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them fatal, have been reported in patients treated with ETORICOXIB BIOTECH. (See section 4.8).

Caution is advised in the elderly, patients using any other NSAID or aspirin (acetylsalicylic acid) concomitantly or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding who are most at risk of developing gastrointestinal complications with NSAIDs such as ETORICOXIB BIOTECH.

The risk of gastrointestinal side effects (gastrointestinal ulceration or other gastrointestinal complications) is further increased when ETORICOXIB BIOTECH is taken concomitantly with aspirin (acetylsalicylic acid) (even at low doses). (See section 4.5).

Hepatic effects

There have been reports of elevations in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (approximately three or more times the upper limit of normal) in approximately 1 % of patients treated for up to one year with ETORICOXIB BIOTECH 60 mg and 90 mg daily.

If a patient present 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, the use of ETORICOXIB BIOTECH should be discontinued.

Medically appropriate supervision should be upheld with the use of ETORICOXIB BIOTECH in the elderly and in patients with renal, hepatic or cardiac dysfunction.

Appropriate steps should be taken if these patients deteriorate during treatment including discontinuation of therapy.

The use of NSAIDs in patients with infection should be done with caution as fever and other signs of inflammation may be masked with the use of ETORICOXIB BIOTECH.

The use of ETORICOXIB BIOTECH is not recommended in women attempting to fall pregnant.

The concomitant use of ETORICOXIB BIOTECH with warfarin or other anticoagulant should be done with caution (see section 4.5).

Considerable cross-sensitivity exist between aspirin and other NSAIDs and it is generally recommended that patients who have had hypersensitivity reactions to aspirin should avoid all NSAIDs including ETORICOXIB BIOTECH (see section 4.3).

Since the tablets contain lactose, ETORICOXIB BIOTECH is not recommended for patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Ciclosporin and tacrolimus:

Concomitant use of ciclosporin or tacrolimus with any NSAID may increase the nephrotoxic effect of ciclosporin or tacrolimus.

When ETORICOXIB BIOTECH and either ciclosporin or tacrolimus are used in combination, renal function should be monitored.

Warfarin:

The use of ETORICOXIB BIOTECH 120 mg daily was associated with an approximate 13 % increase in prothrombin time International Normalized Ratio (INR) in patients stabilised on chronic warfarin therapy.

In patients receiving warfarin or similar medicines, standard monitoring of INR values should be done on initiation of therapy with ETORICOXIB BIOTECH or when therapy is changed.

Rifampicin:

Concomitant use of ETORICOXIB BIOTECH with rifampicin, a potent inducer of hepatic metabolism, produced a 65 % decrease in etoricoxib plasma area under the curve (AUC) and this interaction should be considered when ETORICOXIB BIOTECH is co-administered with rifampicin.

Methotrexate:

When ETORICOXIB BIOTECH at doses greater than 90 mg daily are co-administered with methotrexate, methotrexate-related toxicity should be considered.

Diuretics, Angiotensin Converting Enzyme (ACE) Inhibitors and Angiontensin receptor blockers (ARBs):

The antihypertensive effect of diuretics, ACE inhibitors and ARBs may be diminished by non-selective NSAIDs and COX-2 selective inhibitors such as ETORICOXIB BIOTECH.

This interaction should be given consideration in patients taking ETORICOXIB BIOTECH concomitantly with these medicines.

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 COX-2 inhibitors such as ETORICOXIB BIOTECH, may experience a further deterioration of renal function, including possible acute renal failure with the co-administration of ACE inhibitors or ARBs. These effects may be reversible.

The combination should therefore be administered with caution, especially in the elderly.

Lithium:

Increased plasma lithium levels can occur with concomitant use of NSAIDs and selective COX-2 inhibitors such as ETORICOXIB BIOTECH. This interaction should be considered in patients taking ETORICOXIB BIOTECH concomitantly with lithium (see section 4.3).

Aspirin:

Because of its lack of platelet effects, ETORICOXIB BIOTECH is not a substitute for aspirin for cardiovascular prophylaxis.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with ETORICOXIB BIOTECH.

No effect on the anti-platelet activity of aspirin (81 mg once daily) has been reported in healthy subjects, at steady state, receiving ETORICOXIB BIOTECH 120 mg once daily.

ETORICOXIB BIOTECH can be used concomitantly with low-dose aspirin used for cardiovascular prophylaxis. The concomitant administration of low-dose aspirin with ETORICOXIB BIOTECH may however increase the rate of GI ulceration or other complications compared to use of ETORICOXIB BIOTECH alone.

Concomitant administration of ETORICOXIB BIOTECH with doses of aspirin above those for cardiovascular prophylaxis or with other NSAIDs should be avoided (see section 4.4).

Oral Contraceptives:

ETORICOXIB BIOTECH 60 mg given concomitantly with an oral contraceptive containing 35 µg ethinyl estradiol (EE) and 0,5 mg to 1 mg norethindrone for 21 days increased the steady state $AUC_{0\text{-}24hr}$ of EE by 37 %.

ETORICOXIB BIOTECH 120 mg given with the same oral contraceptive concomitantly or separated by 12 hours increased the steady state $AUC_{0\text{-}24hr}$ of EE by 50 % to 60 %.

When selecting an oral contraceptive for use with ETORICOXIB BIOTECH the increase in EE concentration should be considered.

Increased EE exposure can increase the incidence of adverse events associated with oral contraceptives (e.g. venous thromboembolic events in women at risk).

Furosemide:

ETORICOXIB BIOTECH reduces the natriuretic effect of furosemide and thiazides as a result of the inhibition of renal prostaglandin synthesis (see section 4.4).

Hormone Replacement Therapy:

Administration of ETORICOXIB BIOTECH 120 mg with hormone replacement therapy consisting of conjugated oestrogens (0,625 mg) for 28 days, increased the mean steady state $AUC_{0\text{-}24hr}$ of unconjugated oestrone (41 %), equilin (76 %), and 17-beta-estradiol (22 %).

The effect of the recommended chronic doses of ETORICOXIB BIOTECH (60 mg and 90 mg) has not been studied.

The effects of ETORICOXIB BIOTECH 120 mg on the exposure ($AUC_{0\text{-}24hr}$) to these oestrogenic components of conjugated oestrogens were less than half of those observed when conjugated oestrogens was administered alone and the dose was increased from 0,625 mg to 1,25 mg.

The clinical significance of these increases is unknown**,** and higher doses of conjugated oestrogens were not studied in combination with ETORICOXIB BIOTECH.

These increases in oestrogenic concentration should be taken into consideration when selecting post-menopausal hormone therapy for use with ETORICOXIB BIOTECH because the increase in oestrogen exposure might increase the risk of adverse events associated with Hormone Replacement Therapy (HRT).

Effects of ETORICOXIB BIOTECH on medicines metabolised by sulfotransferases:

ETORICOXIB BIOTECH is an inhibitor of human sulfotransferase activity, particularly SULT1E1, and has been shown to increase the serum concentrations of ethinyl oestradiol.

While knowledge about effects of multiple sulfotransferases is presently limited and the clinical consequences for

many medicines are still being examined, it may be sensible to exercise care when administering ETORICOXIB BIOTECH concurrently with other medicines primarily metabolised by human sulfotransferases (e.g. oral salbutamol and minoxidil).

Effects of ETORICOXIB BIOTECH on digoxin

The steady state plasma $AUC_{0\text{-}24hr}$ or renal elimination of digoxin in healthy volunteers is not altered by a dose of 120 mg etoricoxib one daily for 10 days. Digoxin C_{max} was increased (approximately 33 %) (see section 4.3).

Other:

No clinically important effects on the pharmacokinetic properties of prednisone/prednisolone have been reported with concomitant ETORICOXIB BIOTECH administration.

Antacids did not have clinically important effects on the pharmacokinetic properties of ETORICOXIB BIOTECH.

Ketoconazole, a potent inhibitor of CYP3A4, dosed at 400 mg once a day for 11 days to healthy volunteers did not have any clinically important effect on the single-dose pharmacokinetics of 60 mg ETORICOXIB BIOTECH (43 % increase in AUC).

ETORICOXIB BIOTECH has been used concomitantly with a wide range of commonly prescribed medicines without evidence of clinical adverse interactions.

4.6 Fertility, pregnancy and lactation

ETORICOXIB BIOTECH is contraindicated in pregnancy and lactation (see section 4.3).

Women of child-bearing potential / Contraception in males and females

Fertile women attempting to conceive should not use ETORICOXIB BIOTECH.

Pregnancy

ETORICOXIB BIOTECH, as with other medicines inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester.

Breastfeeding

Mothers taking ETORICOXIB BIOTECH should not breastfeed their babies.

4.7 Effects on ability to drive and use machines

The effect of etoricoxib on the ability to drive or use machines has not been studied. Patients who experience dizziness, vertigo or somnolence while taking ETORICOXIB BIOTECH should refrain from driving or operating machinery.

4.8 Undesirable effects

Infections and infestations	
Frequent:	Alveolar osteitis.
Less frequent:	Gastroenteritis, upper respiratory infection, urinary tract infection.
Blood and lymphatic system disorders	
Less frequent:	Anaemia (primarily associated with gastrointestinal bleeding), leukopenia.
Frequency unknown:	Thrombocytopenia.
Immune system disorders	
Frequency unknown:	Hypersensitivity reactions, including angioedema, anaphylactic/ anaphylactoid reactions including shock.
Metabolism and nutrition disorders	
Frequent:	Oedema/fluid retention.
Less frequent:	Increased or decreased appetite, weight gain.
Psychiatric disorders	
Less frequent:	Anxiety, depression, decreased mental acuity.
Frequency unknown:	Confusion, hallucinations and restlessness.
Nervous system disorders	
Frequent:	Dizziness, headache.
Less frequent:	Insomnia, paraesthesia / hypaesthesia.
Frequency unknown:	Cerebrovascular incidents (stroke), dysgeusia, somnolence.
Eye disorders	
Less frequent:	Conjunctivitis.
Frequency unknown:	Blurred vision.
Ear and labyrinth disorders	
Less frequent:	Tinnitus, vertigo.
Cardiac disorders	

Frequent:	Palpitations.
Less frequent:	Atrial fibrillation, congestive heart failure, non-specific ECG changes, myocardial infarction, angina pectoris.
Frequency unknown:	Aggravated hypertension, dysrhythmia and tachycardia, cardiovascular thrombotic events.
Vascular disorders	
Frequent:	Hypertension.
Less frequent:	Flushing, transient ischaemic attack, hypertensive crisis, vasculitis.
Frequency unknown:	Aggravated hypertension, peripheral oedema, hypertensive crisis.
Respiratory, thoracic and mediastinal disorders	
Less frequent:	Cough, dyspnoea, epistaxis.
Frequency unknown:	Bronchospasms.
Gastrointestinal disorders	
Frequent:	Gastrointestinal disorders (e.g. abdominal pain, flatulence, heartburn), diarrhoea, dyspepsia, epigastric discomfort, nausea.
Less frequent:	Abdominal distention, acid reflux, bowel movement pattern change, constipation, gastritis, vomiting, dry mouth, gastro duodenal ulcer, irritable bowel syndrome, oesophagitis, oral ulcer, pancreatitis.
Frequency unknown:	Peptic ulcers including gastrointestinal perforation and bleeding (mainly in the elderly).
Hepato-biliary disorders	
Frequency unknown:	Hepatitis, jaundice, hepatic failure.
Skin and subcutaneous tissue disorders	
Frequent:	Ecchymosis.
Less frequent:	Facial oedema, pruritus, rash, erythema.

Frequency unknown:	Urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis, fixed medicine eruption, Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) (see section 4.4).
Musculoskeletal, connective tissue and bone disorders	
Less frequent:	Muscular cramp/spasm, musculoskeletal pain/stiffness.
Renal and urinary disorders	
Less frequent:	Proteinuria.
Frequency unknown:	Renal insufficiency, including renal failure, nephrotoxicity including interstitial nephritis and nephrotic syndrome.
General disorders and administration site conditions	
Frequent:	Asthenia/fatigue, flu-like disease.
Less frequent:	Chest pain.
Investigations	
Frequent:	ALT increased, AST increased.
Less frequent:	Blood urea increased, creatine phosphokinase increased, haematocrit decreased, haemoglobin decreased, hyperkalaemia, leukocytes decreased, platelets decreased, serum creatinine increased, uric acid increased, blood sodium decreased.

The following serious undesirable effects have been reported in association with the use of NSAIDs and cannot be ruled out for ETORICOXIB BIOTECH: nephrotoxicity including interstitial nephritis and nephrotic syndrome; hepatotoxicity including hepatic failure and pancreatitis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

The most frequently observed adverse experiences were consistent with the safety profile for ETORICOXIB BIOTECH (e.g. gastrointestinal events, renovascular events).

In the event of overdose, it is reasonable to employ the usual supportive measures, such as removing of unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

ETORICOXIB BIOTECH is not dialysable by haemodialysis and it is not known whether ETORICOXIB BIOTECH is dialysable by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

A. 3.1 Anti-Rheumatics (anti-inflammatory agents)

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, coxibs, ATC Code: M01 AH05

Etoricoxib is a nonsteroidal anti-inflammatory drug (NSAID) that displays anti-inflammatory, analgesic and antipyretic activities in animal models.

Etoricoxib is an orally active selective cyclo-oxygenase-2 (COX-2) inhibitor that inhibits prostaglandin synthesis.

5.2 Pharmacokinetic properties

Absorption

Etoricoxib is well absorbed after oral administration with a mean oral bioavailability of approximately 100 %.

Following administration of 120 mg once-daily dosing to fasted adults, peak plasma concentration (geometric mean C_{max} equal to 3,6 µg/ml) was observed at approximately 1 hour (T_{max}) following to steady state.

The geometric mean AUC_{0-24hr} was 37,8 µg/hr/ml.

The pharmacokinetic properties of etoricoxib are linear across the clinical dose range.

The extent or rate of absorption of a dose of etoricoxib 120 mg is not clinically meaningfully affected by a standard meal.

The pharmacokinetic properties of etoricoxib are similar (comparable AUC, C_{max} within approximately 20 %) when administered alone, with a magnesium/aluminium hydroxide antacid or a calcium carbonate antacid (approximately 50 mEq acid-neutralizing capacity).

Distribution

Etoricoxib is extensively (~92 %) bound to human plasma protein over the range of concentrations of 0,05 µg/ml to 5 µg/ml.

The volume of distribution in humans at steady state (V_{dss}) is approximately 120 litre.

Etoricoxib crosses the placenta and the blood-brain barrier.

Metabolism

Etoricoxib undergoes extensive hepatic metabolism with less than 1 % of a dose recovered in urine as the parent compound.

The major metabolism route to form the 6'-hydroxymethyl derivative is catalysed by cytochrome P450 (CYP) enzymes.

There are five metabolites identified in humans. The principal metabolite is the 6'-carboxylic acid derivative of etoricoxib formed by further oxidation of the 6'-hydroxymethyl derivative.

These principal metabolites have either no measurable activity or are only weakly active as COX-2 inhibitors.

Elimination

Etoricoxib is eliminated mainly through metabolism followed by renal excretion. After the administration of a single radio-labelled 25 mg intravenous dose of etoricoxib, 70 % was recovered in urine and 20 % in faeces, mostly as metabolites. Less than 2 % was recovered as unchanged medicine.

After the administration of 120 mg etoricoxib once-daily, steady state concentrations are reached within seven days with an accumulation ratio of approximately 2, corresponding to an accumulation half-life of approximately 22 hours.

Rate of plasma clearance is estimated to be approximately 50 ml/min.

Special Populations

Elderly

Pharmacokinetic properties in the elderly (65 years of age and older) with normal renal function are similar to those in the young. In clinical studies a higher incidence of adverse experiences was observed in older patients as compared to younger patients (see section 4.2).

Hepatic Insufficiency

The administration of 60 mg etoricoxib once daily to patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) lead to approximately 16 % higher mean AUC as compared to healthy subjects given the same regimen.

The administration of 60 mg etoricoxib ***every other day*** to patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9) had comparable mean AUC to the healthy subjects given etoricoxib 60 mg once daily.

There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score greater than 9). (See sections 4.3 and 4.2).

Renal Insufficiency

The pharmacokinetic properties of a single dose of etoricoxib 120 mg in patients with moderate to severe renal insufficiency and patients with end stage renal disease on haemodialysis were not significantly different from those in healthy subjects.

Haemodialysis contributed insignificantly to elimination (dialysis clearance approximately 50 ml/min).

Paediatric Patients

Studies have not been performed on the pharmacokinetic properties of etoricoxib in paediatric patients (less than 12 years of age).

In a pharmacokinetic study (n=16) conducted in adolescents (aged 12 to 17) the pharmacokinetic properties in adolescents weighing 40 kg to 60 kg given etoricoxib 60 mg once daily and in adolescents greater than 60 kg given etoricoxib 90 mg once daily were similar to the pharmacokinetics in adults given etoricoxib 90 mg once daily.

Safety and efficacy of etoricoxib in paediatric and adolescent patients have not been established (see section 4.3).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Calcium phosphate dibasic (anhydrous)

Croscarmellose sodium

Hydroxypropyl cellulose

Magnesium stearate

Microcrystalline cellulose

Coating:

The 60 mg tablet contains Opadry II 32K510024 Green consisting of:

FD&C Blue #2 / Indigo Carmine Aluminium Lake

HPMC 2910 / Hypromellose

Iron oxide yellow

Lactose monohydrate

Titanium dioxide

Triacetin

The 90 mg tablet contains Opadry II 32K580000 White consisting of:

HPMC 2910 / Hypromellose

Iron oxide yellow

Lactose monohydrate

Titanium dioxide

Triacetin

The 120 mg tablet contains Opadry II 32K510022 Green consisting of:

FD&C Blue #2 / Indigo Carmine Aluminium Lake

HPMC 2910 / Hypromellose

Iron oxide yellow

Lactose monohydrate

Titanium dioxide

Triacetin

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 30 ºC.

Store in the original package.

Protect from moisture.

Keep blisters in outer carton until required for use.

6.5 Nature and contents of container

ETORICOXIB BIOTECH are presented as:

- 8 Tablets Blister of Unprinted Aluminium Foil and Unprinted CFB foil in cardboard box;
- 10 Tablets Blister of Unprinted Aluminium Foil and PVC/PVDC foil in cardboard box;
- 10 Tablets Blister of Unprinted Aluminium Foil and PVC/PE/PVDC foil in cardboard box.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd.

Block K West, Central Park

400 16th Road, Randjespark

Midrand

1685

8. REGISTRATION NUMBER(S)

ETORICOXIB 60 BIOTECH: 50/3.1/0586

ETORICOXIB 90 BIOTECH: 50/3.1/0587

ETORICOXIB 120 BIOTECH: 50/3.1/0588

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 01 September 2020

10. DATE OF REVISION OF THE TEXT

31 August 2021, SAHPRA approval – 06 December 2021