SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ADCO ETORICOXIB 30 mg, film coated tablets

ADCO ETORICOXIB 60 mg, film coated tablets

ADCO ETORICOXIB 90 mg, film coated tablets

ADCO ETORICOXIB 120 mg, film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ADCO ETORICOXIB 30 mg: Each film coated tablet contains 30 mg of etoricoxib.

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

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

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

ADCO ETORICOXIB is sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

ADCO ETORICOXIB 30 mg: Blue-green, apple-shaped, biconvex film coated tablets debossed with ‘30’ on one side and plain on the other, with dimensions of 5,8 x 5,9 mm ± 7,5 %.

ADCO ETORICOXIB 60 mg: Dark-green, apple-shaped, biconvex film coated tablets debossed with ‘60’ on one side and plain on the other, with dimensions of 7,1 x 7,3 mm ± 7,5 %.

ADCO ETORICOXIB 90 mg: White, apple-shaped, biconvex film coated tablets debossed with ‘90’ on one side and plain on the other, with dimensions of 8,1 x 8,3 mm ± 7,5 %.

ADCO ETORICOXIB 120 mg: Pale-green, apple-shaped, biconvex film coated tablets debossed with ‘120’ on one side and plain on the other, with dimensions of 8,9 x 9,2 mm ± 7,5 %.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ADCO ETORICOXIB is indicated for:

- Symptomatic relief of osteoarthritis (OA) and 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

Osteoarthritis

The recommended dose is 30 mg once daily. In some patients with insufficient relief from symptoms, the dose may be increased to 60 mg once daily.

Rheumatoid arthritis

The recommended dose is 90 mg once daily.

Ankylosing spondylitis

The recommended dose is 90 mg once daily.

Acute gouty arthritis

The recommended dose is 120 mg once daily limited to a maximum of 8 days treatment.

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.

Primary Dysmenorrhoea

The recommended dose is 120 mg once daily.

Post-operative dental surgery pain

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, limited to a maximum of 8 days treatment.
- The dose for acute pain and primary dysmenorrhea should not exceed 120 mg daily.
- The dose for post-operative acute dental surgery pain should not exceed 90 mg daily.

As the cardiovascular risks of ADCO ETORICOXIB 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).

Special populations

Elderly

No dosage adjustment is necessary for elderly patients although the elderly may be more susceptible to renal, gastrointestinal and cardiovascular adverse effects (see section 4.4 and 4.8).

Hepatic insufficiency

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

In patients with moderate hepatic dysfunction (Child-Pugh score 7 to 9), regardless of indication, the dose of 30 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, and administration of ADCO ETORICOXIB once daily can also be considered.

Clinical experience is limited particularly in patients with moderate hepatic dysfunction and caution is advised. There are no clinical or pharmacokinetic data in patients with severe hepatic dysfunction (Child-Pugh score > 9) therefore, its use is contraindicated in these patients (see section 4.3).

Renal insufficiency

No dosage adjustment is necessary for patients with creatinine clearance ≥ 30 mL/min. The use of ADCO ETORICOXIB in patients with creatinine clearance < 30 mL/min is contraindicated.

Paediatric patients

ADCO ETORICOXIB is contraindicated in children and adolescents under 16 years of age (see section 4.3).

Method of administration

ADCO ETORICOXIB is administered orally. ADCO ETORICOXIB may be taken with or without food. ADCO ETORICOXIB should be administered for the shortest duration possible and the lowest effective daily dose of ADCO ETORICOXIB should be used.

4.3 Contraindications

ADCO ETORICOXIB is contraindicated in patients with:

- Known hypersensitivity to etoricoxib or any of the ingredients of ADCO ETORICOXIB listed under section 6.1.

- A history of asthma, acute rhinitis, nasal polyps, angioedema or urticaria, after taking aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) including ADCO ETORICOXIB.
- Congestive heart failure (NYHA II-IV).
- Uncontrolled hypertension.
- Heart failure, established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease (see section 4.4).
- Peri-operative analgesia in the setting of coronary artery bypass surgery (CABG).
- Severe hepatic dysfunction (serum albumin <25 g/L or Child-Pugh score >9).
- History of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including ADCO ETORICOXIB.
- Active peptic ulceration or active gastrointestinal (GI) bleeding**.**
- Active or history of recurrent ulcer/ haemorrhage/ perforations.
- Severe renal impairment (estimated creatinine clearance less than 30 mL/min).
- Inflammatory bowel disease.
- Children and adolescents under 16 years of age.
- Pregnancy and lactation.
- Concomitant administration with ADCO ETORICOXIB may lead to toxic blood concentrations of lithium (see section 4.5).
- Digoxin: there was an approximate increase of 33 % in digoxin C_{max} in healthy volunteers (see section 4.5).
- For sulphonamide containing moieties: Known sulphonamide hypersensitivity.

4.4 Special warnings and precautions for use

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

Renal effects

Long-term administration of non-steroidal anti-inflammatory drugs (NSAIDs), such as ADCO ETORICOXIB 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 ADCO 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 and hepatic function in such patients should be considered.

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

Fluid retention, oedema, hypertension

Due to inhibition of prostaglandin synthesis, fluid retention, oedema and hypertension have been observed in patients taking ADCO ETORICOXIB, therefore ADCO ETORICOXIB should 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 ADCO ETORICOXIB, can be associated with new onset or recurrent congestive heart failure.

In view of the product’s inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

Caution is required in patients with a history of hypertension and /or heart failure, left ventricular dysfunction, as fluid retention and oedema have been reported in association with ADCO ETORICOXIB therapy. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of ADCO ETORICOXIB should be taken.

ADCO ETORICOXIB may be associated with more frequent and severe hypertension than some other non-steroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors, particularly at high doses. Therefore, hypertension should be controlled prior to treatment with ADCO ETORICOXIB (see section 4.3) and special attention should be paid to blood pressure monitoring during treatment with ADCO ETORICOXIB. If blood pressure rises significantly, alternative treatment should be considered.

Cardiovascular effects

Reports suggest that the selective COX-2 inhibitor class of medicines such as ADCO ETORICOXIB may be associated with a risk of thrombotic events (especially myocardial infarction (MI) and stroke). As the cardiovascular risks of ADCO ETORICOXIB 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.

Caution is advised when ADCO ETORICOXIB is prescribed to patients with significant cardiovascular risk factors (e.g. hypertension, diabetes mellitus, smoking and hypercholesterolaemia) and should only be treated with ADCO ETORICOXIB after careful

consideration. There appears to be a higher risk for cardiovascular events with higher doses and longer duration of treatment.

Because of its lack of platelet effects, ADCO ETORICOXIB is not a substitute for aspirin for cardiovascular prophylaxis (thromboembolic diseases).

Therefore, antiplatelet therapies should not be discontinued and if indicated should be considered in patients at risk for or with a history of cardiovascular or other thrombotic events.

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

Concomitant administration of low-dose aspirin with ADCO ETORICOXIB increases the rate of gastrointestinal adverse effects (gastrointestinal ulceration, bleeding or perforation) compared to use of ADCO ETORICOXIB alone (see section 4.5).

Serious skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported in association with the use of selective COX-2 inhibitors such as ADCO ETORICOXIB (see section 4.8). Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving ADCO ETORICOXIB (see section 4.8). Some selective COX-2 inhibitors have been associated with an increased risk of skin reactions in patients with a history of any allergy. ADCO ETORICOXIB should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

General

When using ADCO 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 of ADCO ETORICOXIB.
ADCO ETORICOXIB may mask fever and other signs of inflammation or infection.

The use of ADCO ETORICOXIB is not recommended in fertile women attempting to conceive (see section 4.6).

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs including ADCO ETORICOXIB, especially gastrointestinal perforation, ulceration and bleeding (PUBs) which may be fatal.

Caution should be exercised when co-administering ADCO ETORICOXIB with warfarin or other oral anticoagulants (see section 4.5)

Gastrointestinal effects

Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in fatal outcome, have occurred in patients treated with ADCO ETORICOXIB.
Caution is advised with treatment of patients most at risk of developing a gastrointestinal complication with ADCO ETORICOXIB; the elderly, patients using any other non-steroidal anti-inflammatory drug (NSAID) or aspirin concomitantly or patients with a prior history of gastrointestinal disease, such as ulceration, perforation and GI bleeding (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated.

The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with increasing doses of ADCO ETORICOXIB, in patients with a history of ulcers, and the elderly.

When gastrointestinal bleeding or ulceration occurs in patients receiving ADCO ETORICOXIB, treatment with ADCO ETORICOXIB should be stopped.

There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) when ADCO ETORICOXIB is taken concomitantly with aspirin (even at low doses).

Hepatic effects

Any patients 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 signs of hepatic insufficiency occur, or if persistently abnormal liver function tests (three times the upper limit of normal) are detected, ADCO ETORICOXIB should be discontinued.

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as ADCO ETORICOXIB. 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 ADCO ETORICOXIB and evaluate the patient immediately.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per film coated tablet, that is to say essentially 'sodium free'.

4.5 Interactions with other medicines and other forms of interaction

Tacrolimus and ciclosporin

Co-administration of tacrolimus or ciclosporin with any non-steroidal anti-inflammatory drug (NSAID) may increase the nephrotoxic effect of tacrolimus or ciclosporin. Renal function should be monitored when ADCO ETORICOXIB and either of these medicines are used in combination.

Warfarin

In subjects stabilised on chronic warfarin therapy, the administration of etoricoxib 120 mg daily was associated with an approximate 13 % increase in prothrombin time International Normalised Ratio (INR).

Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with ADCO ETORICOXIB is initiated or the dose of ADCO ETORICOXIB is changed.

Anti-coagulants: ADCO ETORICOXIB may enhance the effects of anti-coagulants such as warfarin.

Rifampicin

Co-administration of etoricoxib with rifampicin, a potent inducer of CYP enzymes, produced a 65 % decrease in etoricoxib plasma concentrations. When ADCO ETORICOXIB is co-administered with rifampicin, this interaction may result in recurrence of symptoms. While this information may suggest an increase in dose, doses of ADCO ETORICOXIB greater than those listed for each indication have not been studied in combination with rifampicin and are therefore not recommended (see section 4.2).

Methotrexate

Two studies investigated the effects of etoricoxib 60, 90 or 120 mg administered once daily for seven days in patients receiving once weekly methotrexate doses of 7,5 to 20 mg for rheumatoid arthritis. Etoricoxib at 60 and 90 mg had no effect on methotrexate plasma concentrations (as measured by AUC) or renal clearance. In one study, etoricoxib 120 mg had no effect, but in the other study, etoricoxib 120 mg increased methotrexate plasma concentrations by 28 % and reduced renal clearance of methotrexate by 13 %. Adequate monitoring for methotrexate related toxicity is recommended when ADCO ETORICOXIB at doses greater than 90 mg daily and methotrexate are administered concomitantly.

Diuretics, Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs)

Non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 selective inhibitors such as ADCO ETORICOXIB may reduce the effect of diuretics and other antihypertensive medicines

(diuretics, ACE inhibitors and Angiotensin Receptor Blockers ARB's). This interaction should be taken into consideration in patients taking ADCO ETORICOXIB concomitantly with these products.

In some patients with compromised renal function (e.g. patients who are volume depleted or elderly patients, including those on diuretic therapy), the co-administration of an ACE inhibitor or ARB's may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking ADCO ETORICOXIB concomitantly with ACE inhibitors or ARB's. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Furosemide

Studies have shown that non-steroidal anti-inflammatory drugs (NSAIDs) such as ADCO ETORICOXIB, may reduce the natriuretic and antihypertensive effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Lithium

Non-steroidal anti-inflammatory drugs (NSAIDs) such as ADCO ETORICOXIB have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. Thus, when ADCO ETORICOXIB and lithium are administered concurrently, patients should be observed carefully for signs of lithium toxicity.

Aspirin

Because of its lack of platelet effects, ADCO ETORICOXIB is not a substitute for aspirin for cardiovascular prophylaxis. ADCO ETORICOXIB can be used concomitantly with aspirin at doses used for cardiovascular prophylaxis (low dose aspirin). However, concomitant administration of low dose aspirin with ADCO ETORICOXIB may result in an increased rate of GI ulceration (gastrointestinal ulceration, bleeding or perforation) or other complications compared to use of ADCO ETORICOXIB alone. Concomitant administration of ADCO ETORICOXIB with doses of aspirin above those for cardiovascular prophylaxis or with other non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided.
There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with ADCO ETORICOXIB.

NSAIDs: use of two or more NSAIDs concomitantly could result in an increase in side effects.

Oral contraceptives

An oral contraceptive containing 35 micrograms ethinyl estradiol (EE) and 0,5 to 1 mg norethindrone (NET) given concomitantly with etoricoxib 60 mg for 21 days increased the steady state $AUC_{0\text{-}24hr}$ of EE by 37 %. Etoricoxib 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 %; however, norethindrone (NET) concentrations generally did not increase to a clinically relevant degree. This increase in EE concentration should be considered when selecting an oral contraceptive for use with ADCO ETORICOXIB. An increase in EE exposure can increase the incidence of adverse events associated with oral contraceptives (e.g. venous thromboembolic events in women at risk).

Hormone Replacement Therapy

Hormone replacement therapy consisting of 0,625 mg conjugated estrogens administered with etoricoxib 120 mg for 28 days, increased the mean steady state AUC_{0-24hr} of unconjugated estrone (41 %), equilin (76 %), and 17-β- estradiol (22 %). The effect of the recommended chronic doses of etoricoxib 30 mg and 60 mg has not been studied. The effects of etoricoxib 120 mg on the exposure (AUC_{0-24hr}) to these estrogenic components of conjugated estrogens were less than half of those observed, when conjugated estrogens were administered alone, and the dose was increased from 0,625 to 1,25 mg. The clinical significance of these increases are unknown, and higher doses of conjugated oestrogens have not been studied in combination with etoricoxib. These increases in estrogenic concentration should be taken into consideration when selecting post-menopausal hormone replacement therapy for use with ADCO ETORICOXIB because the increase in estrogen exposure might increase the risk of adverse events associated with hormone replacement therapy (HRT).

Effect of ADCO ETORICOXIB on medicines metabolised by sulfotransferases

ADCO ETORICOXIB is an inhibitor of human sulfotransferase activity, particularly SULT1E1, and has been shown to increase the serum concentrations of ethinyl estradiol. While knowledge about effects of multiple sulfotransferases is presently limited and the clinical consequences for many medicines are still being examined, it may be prudent to exercise care when administering ADCO ETORICOXIB concurrently with other medicines primarily metabolised by human sulfotransferases (e.g. oral salbutamol and minoxidil).

Digoxin

Etoricoxib 120 mg administered once daily for 10 days did not alter the steady state plasma $AUC_{0\text{-}24hr}$ or renal elimination of digoxin. There was an increase in digoxin C_{max} (approximately 33 %). This increase is not generally important for most patients. However, patients at high risk of digoxin toxicity should be monitored for this when ADCO ETORICOXIB and digoxin are administered concomitantly.

Prednisone/ prednisolone

In interaction studies, etoricoxib did not have clinically important effects on the pharmacokinetics of prednisone/ prednisolone.

Corticosteroids: increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs).

Antacids

Antacids did not affect the pharmacokinetics of ADCO ETORICOXIB to a clinically relevant extent.

Ketoconazole

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

Voriconazole and Miconazole

Co-administration of either oral voriconazole or topical miconazole oral gel, strong CYP3A4 inhibitors, with etoricoxib caused a slight increase in exposure to etoricoxib but is not considered to be clinically meaningful based on published data.

Anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs):

Anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding.

4.6 Fertility, pregnancy and lactation

Pregnancy

ADCO ETORICOXIB is contraindicated in pregnancy. If a woman becomes pregnant during treatment, ADCO ETORICOXIB must be discontinued (see section 4.3).

Use of NSAIDs, including ADCO ETORICOXIB, can cause premature closure of the foetal ductus arteriosus and foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment.

Regular use of non-steroidal anti-inflammatory drugs (NSAIDs) during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus *in utero*, and possible, in persistent pulmonary hypertension to the new-born. The onset of labour may be delayed and its duration increased.

Lactation

Safety in lactation has not been established.

Fertility

The use of ADCO ETORICOXIB is not recommended in women attempting to conceive.

4.7 Effects on ability to drive and use machines

ADCO ETORICOXIB has a moderate influence on the ability to drive and use machines (see section 4.8).

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

4.8 Undesirable effects

a. Summary of the safety profile

The most commonly observed adverse events are gastrointestinal in nature.

b. Tabulated summary of adverse reactions

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
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, thrombocytopenia.
Immune system disorders	Less frequent	hypersensitivity, angioedema/ anaphylactic reactions including shock.
	Frequent	oedema/fluid retention.

Metabolism and nutrition disorders	Less frequent	appetite increase or decrease, weight gain.
Psychiatric disorders	Less frequent	anxiety, depression, mental acuity decreased, hallucinations, confusion, restlessness.
Nervous system disorders	Frequent	dizziness, headache.
	Less frequent	dysgeusia, insomnia, paraesthesia/ hypaesthesia, somnolence.
Eye disorders	Less frequent	blurred vision, conjunctivitis.
Ear and labyrinth disorders	Less frequent	tinnitus, vertigo.
Cardiac disorders	Frequent	palpitations, dysrhythmia.
	Less frequent	atrial fibrillation, tachycardia, congestive heart failure, nonspecific ECG changes, angina pectoris, myocardial infarction.
	Frequency unknown	peripheral oedema, cardiovascular thrombotic events, hypertension, and cardiac failure.
Vascular disorders	Frequent	hypertension.
	Less frequent	flushing, cerebrovascular incidents (stroke), transient ischaemic attack, hypertensive crisis, vasculitis.
	Frequency unknown	aggravated hypertension.

Respiratory, thoracic and mediastinal disorders	Frequent	bronchospasm.
	Less frequent	cough, dyspnoea, epistaxis.
Gastrointestinal disorders	Frequent	abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, constipation, flatulence, gastritis, heartburn/acid reflux, diarrhoea, dyspepsia/ epigastric discomfort, nausea, vomiting, oesophagitis, oral ulcer.
	Less frequent	abdominal distention, bowel movement pattern change, dry mouth, gastroduodenal ulcer, peptic ulcers including gastrointestinal perforation and bleeding, irritable bowel syndrome, pancreatitis.
Hepato-biliary disorders	Frequent	ALT increased, AST increased.
	Less frequent	hepatitis, hepatic failure, jaundice.
Skin and subcutaneous tissue disorders	Frequent	ecchymosis.
	Less frequent	facial oedema, pruritus, rash, erythema, urticaria, bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, fixed drug eruption, Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) (see section 4.4).

Musculoskeletal and connective tissue disorders	Less frequent	muscular cramp/spasm, musculoskeletal pain/stiffness.
Renal and urinary disorders	Less frequent	proteinuria, serum creatinine increased, renal failure/renal insufficiency.
General disorders and administrative site conditions	Frequent	asthenia/fatigue, flu-like disease.
	Less frequent	chest pain.
Investigations	Less frequent	increased blood urea, creatine phosphokinase increased, decreased haematocrit, decreased haemoglobin, decreased hyperkalaemia, decreased leukocytes, decreased platelets, uric acid increased, blood sodium decreased.

Post-marketing

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Blood and lymphatic system disorders	Frequency unknown	thrombocytopenia

Immune system disorder	Frequency unknown	hypersensitivity reactions including angioedema, anaphylactic/ anaphylactoid reactions including shock.
Psychiatric disorders	Frequency unknown	confusion, hallucinations, depression, restlessness.
Nervous system disorder	Frequency unknown	dysgeusia, somnolence.
Eye disorders	Frequency unknown	blurred vision.
Cardiac disorders	Frequency unknown	congestive heart failure, palpitations, angina, dysrhythmia.
Vascular disorders	Frequency unknown	hypertensive crisis.
Respiratory, thoracic and mediastinal disorders	Frequency unknown	bronchospasm.
Gastrointestinal disorders	Frequency unknown	abdominal pain, oral ulcers, peptic ulcers including gastrointestinal perforation and bleeding (mainly in the elderly), vomiting, diarrhoea.
Hepato-biliary disorders	Frequency unknown	hepatitis, jaundice, hepatic failure.
Skin and subcutaneous tissue disorders	Frequency unknown	angioedema, pruritus, erythema, rash urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, fixed drug eruption.

Renal and urinary disorders	Frequency unknown	renal insufficiency, including renal failure.

c. Description of selected adverse reactions

No information available.

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

The most frequently observed adverse effects were gastrointestinal events and renovascular events.

Treatment

In the event of overdose, it is reasonable to employ the usual supportive measures, e.g. remove unabsorbed material from the GI tract, employ clinical monitoring, and institute supportive therapy, if required.

ADCO ETORICOXIB is not dialysable by haemodialysis; it is not known whether ADCO ETORICOXIB is dialysable by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 3.1 Antirheumatics (anti-inflammatory agents).

Etoricoxib is a non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic activities in animal models. Etoricoxib is an orally active, selective cyclo-oxygenase-2 (COX-2) inhibitor.

5.2 Pharmacokinetic properties

Absorption

Orally administered etoricoxib is well absorbed. The absolute bioavailability is approximately 100 %. Following 120 mg once daily dosing to steady state, the peak plasma concentration (geometric mean C_{max} = 3,6 µg/mL) was observed at approximately 1 hour (T_{max}) after administration to fasted adults. The geometric mean area under the curve ($AUC_{0\text{-}24hr}$) was 37,8 µg•hr/mL. The pharmacokinetics of etoricoxib are linear across the clinical dose range.

After administration of a 120 mg dose, dosing with a standard meal has no clinical effect on the extent of absorption of etoricoxib. In clinical trials, etoricoxib was administered without regard to food.

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

Distribution

Etoricoxib is approximately 92 % bound to human plasma protein over the range of concentrations of 0,05 to 5 µg/mL.

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

Etoricoxib crosses the placenta and the blood-brain barrier.

Biotransformation

Etoricoxib is extensively metabolised in the liver with < 1 % of a dose recovered in urine as the parent compound. The major route of metabolism to form the 6'-hydroxymethyl derivative is catalysed by cytochrome P450 (CYP) enzymes. CYP3A4 appears to contribute to the metabolism of etoricoxib *in vivo*. *In vitro* studies indicate that CYP2D6, CYP2C9, CYP1A2 and CYP2C19 also can catalyse the main metabolic pathway, but their quantitative roles *in vivo* have not been studied.

Five metabolites have been identified in humans. Metabolism *in vitro* involves conversion primarily to the 6'-hydroxymethyl derivative. The 6'-hydroxymethyl derivative is further metabolised by oxidation to the principal metabolite, the 6'-carboxylic acid derivative of etoricoxib. These principal metabolites either demonstrate no measurable activity or are only weakly active as COX-2 inhibitors.

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 120 mg, with an accumulation ratio of approximately 2, corresponding to a half-life of approximately 22 hours. The plasma clearance after a 25 mg intravenous dose is estimated to be approximately 50 mL/min.

Elderly

Pharmacokinetics in the elderly (65 years of age and older) with normal renal function are similar to those in the young. A higher incidence of adverse experiences can be expected in older patients compared to younger patients. No dosage adjustment is necessary for elderly patients (for elderly patients with hepatic impairment (see section 4.2).

Hepatic Insufficiency

Patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) administered etoricoxib 60 mg once daily (for 21 days) had an approximately 16 % higher mean AUC as compared to healthy subjects given the same regimen. Patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9) administered etoricoxib 60 mg every other day (for 21 days) had similar mean AUC to the healthy subjects given etoricoxib 60 mg once daily; etoricoxib 30 mg once daily has not been studied in this population. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score > 9) (see sections 4.2 and 4.3).

Renal insufficiency

The pharmacokinetics of a single dose of etoricoxib 120 mg in patients with moderate (creatinine clearance 30 to 50 mL/min) to severe (creatinine clearance less than 30 mL/min) of renal insufficiency and patients with end-stage renal disease on haemodialysis were not significantly different from those in healthy subjects. Haemodialysis contributed negligibly to elimination (dialysis clearance approximately 50 mL/min).

Paediatric Patients

The pharmacokinetics of etoricoxib in paediatric patients (less than 12 years of age) has not been studied.

Studies indicate that the pharmacokinetics 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).

5.3 Preclinical safety data

No information available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each ADCO ETORICOXIB film coated tablet contains:

Calcium hydrogen phosphate (anhydrous)

Croscarmellose sodium

Magnesium stearate (E470b)

Microcrystalline cellulose (E460)

ADCO ETORICOXIB 30 mg, 60 mg and 120 mg is coated with the following ingredients:

Glycerol monostearate (E471)

Indigo carmine aluminium lake (E132)

Polyvinyl alcohol (E1203)

Sodium laurylsulfate

Talc (E553b)

Titanium dioxide (E171)

Yellow iron oxide (E172)

ADCO ETORICOXIB 90 mg is coated with the following ingredients:

Glycerol monostearate (E471)

Polyvinyl alcohol (E1203)

Sodium laurylsulfate

Talc (E553b)

Titanium dioxide (E171)

6.2 Incompatibilities

No data available.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

ADCO ETORICOXIB should be stored at or below 25 ºC.

Store in the original package.

6.5 Nature and contents of container

ADCO ETORICOXIB 30 mg, 60 mg, 90 mg, and 120 mg film coated tablets are packed in Aluminium-Aluminium blisters formed of:

- Aluminium forming foil consisting of a 50 µm aluminium layer coated with a 25 µm OPA (oriented polyamide) film coated aluminium layer on one side and 60 µm polyvinyl chloride (PVC) on the other side,

- an aluminium lidding foil consists of a 25 µm or 30 µm aluminium layer coated with a print primer for better printing performance on one side and with a heat-seal lacquer composed of vinyl acrylic resins on the other side.

Pack sizes:

ADCO ETORICOXIB 30 mg: 2, 7, 14, 20, 28, 49 tablets or multi-packs containing 98 (2 packs of 49) tablets.

ADCO ETORICOXIB 60 mg, 90 mg and 120 mg: 2, 5, 7, 10, 14, 20, 28, 30, 49, 50, 84, 100 tablets or multi-packs containing 98 (2 packs of 49) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road,

Erand Gardens,

Midrand,

1685.

Customer Care: 0860 ADCOCK 232625

8. REGISTRATION NUMBER(S)

ADCO ETORICOXIB 30 mg: 50/3.1/0300

ADCO ETORICOXIB 60 mg: 50/3.1/0301

ADCO ETORICOXIB 90 mg: 50/3.1/0302

ADCO ETORICOXIB 120 mg: 50/3.1/0303

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 February 2017

10. DATE OF REVISION OF THE TEXT

09 January 2023

adcock ingram

PI PRM-000491 0118103 03/2023