PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

CORICIB 30 mg Film coated tablets

CORICIB 60 mg Film coated tablets

CORICIB 90 mg Film coated tablets

CORICIB 120 mg Film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CORICIB 30 mg

Each film coated tablet contains etoricoxib 30 mg.

Contains sugar: lactose monohydrate 1,05 mg/coated tablet.

CORICIB 60 mg

Each film coated tablet contains etoricoxib 60 mg.

Contains sugar: lactose monohydrate 2,10 mg/coated tablet.

CORICIB 90 mg

Each film coated tablet contains etoricoxib 90 mg.

Contains sugar: lactose monohydrate 3,15 mg/coated tablet.

CORICIB 120 mg

Each film coated tablet contains etoricoxib 120 mg.

Contains sugar: lactose monohydrate 4,20 mg/coated tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

CORICIB 30 mg

Blue green, film coated, round biconvex tablets, E30 debossed on one side and plain on other side.

CORICIB 60 mg

Green to dark green, film coated, round biconvex tablets, E60 debossed on one side and plain on other side.

CORICIB 90 mg

White to off white, film coated, round biconvex tablets, E90 debossed on one side and plain on other side.

CORICIB 120 mg

Light green to pale green, film coated round biconvex tablets, E120
debossed on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CORICIB 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

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

Osteo-arthritis (OA): 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 (RA): The recommended dose is 90 mg once daily. In some patients, 60 mg once daily may provide adequate therapeutic benefit.

Ankylosing Spondylitis: The recommended dose is 90 mg once daily. In some patients, 60 mg once daily may provide adequate therapeutic benefit.

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.

Acute Gouty Arthritis: The recommended dose is 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 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.

The dose for acute pain and primary dysmenorrhoea should not exceed 120 mg daily.

The dose for postoperative acute dental surgery pain should not exceed

90 mg daily.

As the cardiovascular risks of CORICIB 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 in CORICIB is necessary for the elderly. Although the elderly may be more susceptible to renal, gastrointestinal and cardiovascular adverse effects (see section 4.4). When using CORICIB in the elderly and in patients with renal, hepatic or cardiac dysfunction, medically appropriate supervision should be intensified.

If these patients show deterioration during treatment, appropriate measures should be taken, including discontinuation of CORICIB.

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, administration of CORICIB 30 mg* once daily can also be considered.

Clinical experience is limited particularly in patients with moderate hepatic dysfunction. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score > 9), therefore the use of CORICIB is contraindicated in these patients (see section 4.3 and 5.2)

Renal Insufficiency

No dosage adjustment is necessary for patients with lesser degrees of renal insufficiency (creatinine clearance ≥ 30 mL/min). The use of CORICIB in patients with creatinine clearance < 30 mL/min is contraindicated (see section 4.3).

When using CORICIB 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 CORICIB.

4.3 Contraindications

CORICIB is contraindicated in:

- patients with known hypersensitivity to any of the excipients of CORICIB (see section 6.1)
- patients with active peptic ulceration or gastrointestinal (GI) bleeding
- patients with severe hepatic dysfunction (Child-Pugh score > 9 or serum albumin < 25 g/litre)
- patients with estimated creatinine clearance < 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 etoricoxib, as contained in CORICIB

- uncontrolled hypertension
- pregnancy and lactation, avoid prescribing NSAIDs such as CORICIB after 20 weeks as it may cause rare kidney problems in unborn babies (see section 4.4)
- 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, peripheral arterial disease and/or cerebrovascular disease (see section 4.4).
- peri-operative analgesia in the setting of coronary artery bypass surgery (CABG).
- Lithium therapy

  Concomitant administration with CORICIB may lead to toxic blood concentration 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 warning an precautions for use

CORICIB 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 CORICIB, are associated with an increased risk of arterial thrombotic
events (especially myocardial infarction (MI)) and stroke).

Long-term administration of NSAIDs such as CORICIB, 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 CORICIB

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 liver cirrhosis. Monitoring of renal and hepatic function in such patients is indicated.

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

Fluid retention, oedema and hypertension have been reported in patients taking CORICIB. All non-steroidal anti-inflammatory drugs (NSAIDs), including CORICIB, can be associated with new onset or recurrent congestive heart failure. Caution should be exercised in patients with a history of cardiac failure, left ventricular dysfunction or hypertension, and in patients with pre-existing oedema from any other reason. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of CORICIB should be taken.

CORICIB may be associated with more frequent and severe hypertension than other NSAIDs and other selective COX-2 inhibitors. Therefore special attention should be paid to blood pressure monitoring during treatment with CORICIB. If blood pressure rises significantly, alternative treatment should be considered.

Reported clinical studies suggest that the selective COX-2 inhibitor class of medicines such as etoricoxib, are associated with an increased risk of thrombotic events [especially myocardial infraction (MI) and stroke]. As the cardiovascular risks of selective COX-2 inhibitors such as etoricoxib as contained in CORICIB 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. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with CORICIB after careful consideration.

CORICIB is not a substitute for aspirin for cardiovascular prophylaxis because of its lack of effect on platelets. Because CORICIB does not inhibit platelet aggregation, anti-platelet 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 CORICIB. For more details, refer to section on interactions (section 4.5).

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 etoricoxib during post-marketing surveillance. Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving etoricoxib (see section 4.8).

Selective COX-2 inhibitors, such as CORICIB have been associated with an increased risk of skin reactions in patients with a history of any allergy. CORICIB should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

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

Gastrointestinal effects

Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in fatal outcome, have occurred in patients treated with etoricoxib.

Caution is advised with treatment of patients at risk of developing a gastrointestinal complication with CORICIB; the elderly, patients using any other NSAIDs or aspirin (acetylsalicylic acid) concomitantly or patients with a prior history of gastrointestinal disease, such as perforation, ulceration and gastrointestinal bleeding.

There is an increase in risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) when CORICIB is taken concomitantly with aspirin (even at low doses).

Elevations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (approximately 3 or more times the upper limit of normal) have been reported in approximately 1 % of patients in clinical trials, treated for up to 1 year with etoricoxib 60 mg and 90 mg daily.

Any 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 (3 times the upper limit of normal) are detected, CORICIB should be discontinued.

CORICIB may mask fever and other signs of inflammation or infection.

Due to inhibition of prostaglandin synthesis, fluid retention and oedema have been reported in patients taking etoricoxib as contained in CORICIB; therefore CORICIB 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 CORICIB, can be associated with new onset or recurrent congestive heart failure (see section 4.8).

The use of CORICIB is not recommended in fertile women attempting to conceive.

Neonatal renal impairment and Oligohydramnios:

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) such as CORICIB around 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation. In some reported postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required. If NSAID treatment is determined necessary, limit use to the lowest effective dose and shortest duration possible. Avoid prescribing NSAIDs at 20 weeks and later in pregnancy because of the additional risk of premature closure of the fetal ductus arteriosus. Consider ultrasound monitoring of amniotic fluid if NSAID treatment extends beyond 48 hours. Discontinue the NSAID if oligohydramnios occurs (see section 4.3 and 4.6).

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

Lactose:

CORICIB 30, 60, 90 and 90 mg tablets contain 1,05 ; 2,10; 3,15 and 4,20 mg lactose, respectively. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take CORICIB.

4.5 Interaction with other medicines and other forms of interaction

Ciclosporin and tacrolimus: Co-administration of ciclosporin or tacrolimus with any NSAID, including CORICIB, may increase the nephrotoxic effect of ciclosporin or tacrolimus. Renal function should be monitored when CORICIB and either of these medicines is 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). Standard monitoring of INR values should be conducted when therapy with CORICIB is initiated or changed in patients receiving warfarin or similar medicines.

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

Methotrexate: Two reported studies investigated the effects of etoricoxib 60 mg, 90 mg or 120 mg administered once daily for 7 days, in patients receiving once-weekly methotrexate doses of 7,5 mg to 20 mg for rheumatoid arthritis. Etoricoxib at 60 mg and 90 mg had no effect on methotrexate plasma concentrations (as measured by AUC) or renal clearance. ln one reported study, etoricoxib 120 mg had no effect on methotrexate plasma concentrations (as measured by AUC) or renal clearance. In the other study, etoricoxib 120 mg increased methotrexate plasma concentrations by 28 % (as measured by AUC) and reduced renal clearance of

methotrexate by 13 %. Monitoring for methotrexate-related toxicity should be considered, when CORICIB at doses > 90 mg daily and methotrexate are administered concomitantly.

Diuretics, Angiotensin Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs): Reports suggest that non-selective NSAIDs and COX-2 selective inhibitors such as etoricoxib, as contained in CORICIB may diminish the antihypertensive effect of diuretics, ACE inhibitors and Angiotensin Receptor Blockers (ARBs). This interaction should be given consideration in patients taking CORICIB concomitantly with these medicines.

In 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 CORICIB, the co-administration of ACE inhibitors or ARBs may result in a further deterioration of renal function, including possible acute renal failure. These effects may be reversible. Therefore, the combination should be administered with caution, especially in the elderly and in patients with impaired renal function. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Lithium: CORICIB may increase plasma lithium levels. This interaction should be given consideration in patients taking CORICIB concomitantly with lithium.

Aspirin: In a reported study in healthy subjects, at steady state, etoricoxib 120 mg once daily had no effect on the anti-platelet activity of aspirin (81 mg once daily). CORICIB may be used concomitantly with aspirin at doses used for cardiovascular prophylaxis (low-dose aspirin). However, concomitant administration of low-dose aspirin with CORICIB increases the rate of gastrointestinal ulceration, and other complications compared to use of etoricoxib alone. Concomitant administration of CORICIB with doses of aspirin above those for cardiovascular prophylaxis or with other NSAIDs should be avoided (see section 4.4).

Concurrent use of aspirin does not mitigate the increased risk of serious cardiovascular thrombotic events associated with CORICIB.

Oral Contraceptives: Etoricoxib 60 mg given concomitantly with an oral contraceptive containing 35 µg ethinyl estradiol (EE) and 0,5 mg to 1 mg norethindrone (NET) for 21 days, increased the steady state AUC_{0-24h} of EE by 37 %. Etoricoxib 120 mg given with the same oral contraceptive concomitantly or separated by 12 hours, increased the steady state AUC_{0-24h} of EE by 50 % to 60 %; however, (NET) concentrations generally did not increase to a clinically relevant degree. This increase in EE concentration should be considered when selecting an appropriate oral contraceptive for use with CORICIB. 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).

Furosemide: Reported clinical studies have shown that NSAIDs such as etoricoxib, as contained in CORICIB reduce the natriuretic and antihypertensive effect of furosemide and thiazides in patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Hormone Replacement Therapy: Administration of etoricoxib 120 mg with hormone replacement therapy consisting of conjugated oestrogens (0,625 mg conjugated oestrogens for 28 days, increased the mean steady state AUC_{0-24h} of unconjugated oestrone (41 %), equilin (76 %) and 17-beta-estradiol (22 %). The effect of the recommended chronic doses of etoricoxib (60 mg and 90 mg) has not been studied. The effects of etoricoxib 120 mg on the exposure (AUC_{0-24h}) 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. These increases in oestrogenic concentration should be taken into consideration when

selecting postmenopausal hormone therapy for use with CORICIB, because the increase in oestrogen exposure might increase the risk of adverse events associated with Hormone Replacement Therapy (HRT).

Effects of etoricoxib on medicines metabolised by sulfotransferases: Etoricoxib 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 prudent to exercise care when administering CORICIB concurrently with other medicines primarily metabolised by human sulfotransferases (e.g. oral salbutamol and minoxidil).

Etoricoxib 120 mg once daily for 10 days in healthy volunteers did not alter the steady state plasma $AUC_{0\text{-}24h}$ or renal elimination of digoxin. There was an increase in digoxin C_{max} (approximately 33 %) (See section 4.3).

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

Antacids do not have clinically significant effects on the pharmacokinetics of CORICIB.

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 (43 % increase in AUC).

4.6 Fertility, pregnancy and lactation

CORICIB is contraindicated in pregnancy and lactation (see section 4.3)

Pregnancy

CORICIB, as in other medicines inhibiting prostaglandin synthesis may cause uterine inertia and premature ductus arteriosis during the last trimester of pregnancy.

Pregnant women should not use CORICIB at 20 weeks or later unless specifically advised to do so by health care professional because these medicines may cause foetal renal dysfunction (see section 4.3 and 4.4)

Breastfeeding:

Mothers on CORICIB should not breastfeed their infants.

Fertility:

The use of CORICIB is not recommended in fertile women attempting to conceive.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a) Summary of the safety profile

The following serious undesirable effects have been reported in association with the use of NSAIDs and cannot be ruled out for etoricoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome; hepatotoxicity including hepatic failure, and pancreatitis. In clinical studies, a higher incidence of adverse experiences was seen in older patients compared to younger patients.

b) Tabulated summary of adverse reactions

System organ class (SOC)	**Frequency**	**Adverse reaction**
Infections and infestations	Frequent Less frequent	Alveolar osteitis Gastroenteritis, upper respiratory infection, urinary tract infection
Blood and lymphatic system disorders	Less frequent Frequency unknown	Anaemia, leukopenia Thrombocytopenia
Immune system disorders	Frequency unknown	Hypersensitivity reactions, including angioedema, anaphylactic/anaphylactoid reactions including shock
Metabolism and nutrition disorders	Frequent Less frequent	Oedema/fluid retention Appetite increase or decrease, weight gain
Psychiatric disorders	Less frequent Frequency unknown	Anxiety, depression, mental acuity decreased Confusion, hallucinations, depression, restlessness
Nervous system disorders	Frequent Less frequent	Dizziness, headache Insomnia, paraesthesia/ hypaesthesia Dysgeusia, somnolence

	Frequency unknown	
Eye disorders	Less frequent Frequency unknown	Conjunctivitis Blurred vision
Ear and labyrinth disorders	Less frequent	Tinnitus, vertigo
Cardiac disorders	Frequent Less frequent Frequency unknown	Palpitations Atrial fibrillation, congestive heart failure, non-specific EGG changes, myocardial infarction, angina Aggravated hypertension, dysrhythmia cardiovascular thrombotic events and tachycardia
Vascular disorders	Frequent Less frequent Frequency unknown	Hypertension Flushing, cerebrovascular incidents (stroke), transient ischaemic attack, vasculitis Hypertensive crisis, peripheral oedema, aggravated hypertension

Respiratory, thoracic and mediastinal disorders	Less frequent Frequency unknown	Cough, dyspnoea, epistaxis Bronchospasm
Gastrointestinal disorders	Frequent Less frequent Frequency unknown	Gastrointestinal disorders (e.g. abdominal pain, flatulence, heartburn), diarrhoea, dyspepsia, epigastric discomfort, nausea Abdominal distension, acid reflux, bowel movement pattern change, constipation, dry mouth, gastroduodenal ulcer, irritable bowel syndrome, oesophagitis, oral ulcer, vomiting, gastritis, pancreatitis Peptic ulcers including gastro-intestinal perforation and bleeding (mainly in the elderly)
Hepato-biliary disorders	Frequent Frequency unknown	Increased ALT and AST Hepatitis, jaundice, hepatic failure
Skin and subcutaneous tissue disorders	Frequent Less frequent	Ecchymosis Facial oedema, pruritus, rash, erythema

	Frequency unknown	Urticaria, Stevens Johnson syndrome, toxic epidermal necrolysis, fixed drug eruption, Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) [see Warnings and Precautions]
Musculoskeletal, connective tissue and bone disorders	Less frequent	Muscular cramp/spasm, musculoskeletal pain/stiffness
Renal and urinary disorders	Less frequent Frequency unknown	Proteinuria, increased serum creatinine Renal insufficiency, including renal failure (see section 5.2) nephrotoxicity including interstitial nephritis and nephrotic syndrome
General disorders and administration site conditions	Frequent Less frequent	Asthenia/fatigue, flu like disease Chest pain
Investigations	Less frequent	Increased blood urea, increased creatine phosphokinase, decreased haematocrit, decreased haemoglobin, hyperkalaemia, decreased leukocytes, decreased platelets, increased uric acid, decreased blood sodium.

c) Description of selected adverse reactions

CORICIB may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are reported, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation (see section 4.3 and 4.4).

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 provders 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 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 dialysable by haemodialysis; it is not known whether etoricoxib is dialysable by peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.3.1 Anti-Rheumatics (Anti-inflammatory Agents). ATC code: M01 AH05

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 absorbed with a mean oral bioavailability of 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 AUC_{0-24h} was 37,8 µg/h/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 120 mg. In reported clinical trials, etoricoxib was administered without regard to food.

The pharmacokinetics of etoricoxib in 12 healthy subjects (40 to 65 years of age) 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

In humans, etoricoxib is approximately 92 % bound to plasma protein over the range of concentrations of 0,05 µg/mL to 5 µg/mL. The volume of distribution at steady state (V_{dss}) is approximately 120 litre. Etoricoxib crosses the placenta and the blood-brain barrier.

Metabolism

Etoricoxib is extensively metabolised in the liver 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.

Elimination

Following administration of a single 25 mg radio-labelled intravenous dose of etoricoxib to healthy subjects, 70 % of radioactivity was recovered in urine and 20 % in faeces, mostly as metabolites. Plasma and urine were collected for 7 days and stool collected for 10 days post-dose. Less than 2 % was recovered as unchanged drug.

Elimination of etoricoxib occurs almost exclusively through metabolism followed by renal excretion. Steady state concentrations of etoricoxib are reached within 7 days of once-daily administration of 120 mg, 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 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. In reported clinical studies, a higher incidence of adverse experiences was seen in older patients compared to younger patients (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. There are no available clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score > 9) [see section 4.2 & 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 of < 30 mL/min) 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 Population

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

In a pharmacokinetic study (N=16) reported in adolescents (aged 12 to 17) the pharmacokinetics in adolescents weighing 40 kg to 60 kg given etoricoxib 60 mg once daily and in adolescents > 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

- Cellulose microcrystalline
- calcium hydrogen phosphate anhydrous
- croscarmellose sodium
- magnesium stearate

Coating:

30 mg: Opadry II green 32K510020 (lactose monohydrate, hypromellose, titanium dioxide, triacetin, indigo carmine aluminium lake, iron oxide yellow)

60 mg: Opadry II green 35K510000 (lactose monohydrate, hypromellose, titanium dioxide, triacetin, indigo carmine aluminium lake, iron oxide yellow)

90 mg: Opadry II white 35K580003 (lactose monohydrate, hypromellose, titanium dioxide, triacetin)

120 mg: Opadry II green 32K510018 (lactose monohydrate, hypromellose, titanium dioxide, triacetin, indigo carmine aluminium lake, iron oxide yellow)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

Store at or below 25 °C.

6.4 Special precautions for storage

Protect from moisture. Keep blister in carton until required for use.

6.5 Nature and contents of container

The tablets are packed in cold form blisters. Each blister strip contains

7 tablets. Carton contains 7 or 28 tablets.

Cold form blister pack

Cold form blister pack comprises of cold form blister laminate composed of oriented polyamide, aluminium foil and PVC film with backing of hard tempered aluminium foil coated with heat seal lacquer on the inner side.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road, Stormill, Ext.1,

Roodepoort, 1724

South Africa

8 REGISTRATION NUMBERS

CORICIB 30 mg: 51/3.1/1148.1144

CORICIB 60 mg: 51/3.1/1149.1145

CORICIB 90 mg: 51/3.1/1150.1146

CORICIB 120 mg: 51/3.1/1151.1147

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: February 2020

10 DATE OF REVISION OF THE TEXT

21 January 2022