

**PROFESSIONAL INFORMATION FOR**

**ETORICOXIB CIPLA 60**

**ETORICOXIB CIPLA 90**

**ETORICOXIB CIPLA 120**

**SCHEDULING STATUS**

**S3**

**1. NAME OF THE MEDICINE**

**ETORICOXIB CIPLA 60** (60 mg, film-coated tablets)

**ETORICOXIB CIPLA 90** (90 mg, film-coated tablets)

**ETORICOXIB CIPLA 120** (120 mg, film-coated tablets)

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

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

Contains sugar: Lactose monohydrate (2,8 mg).

ETORICOXIB CIPLA 90: Each film-coated tablet contains etoricoxib 90 mg

Contains sugar: Lactose monohydrate (4,2 mg).

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

Contains sugar: Lactose monohydrate (5,6 mg).

For the full list of excipients, see **section 6.1**.

### 3. PHARMACEUTICAL FORM

ETORICOXIB CIPLA 60: White to off-white, apple shaped, biconvex film-coated tablet debossed with “C2” on one side and plain on the other side.

ETORICOXIB CIPLA 90: Dark green, apple shaped, biconvex film-coated tablet debossed with “C3” on one side and plain on the other side.

ETORICOXIB CIPLA 120: Dark green, apple shaped, biconvex film-coated tablet debossed with “C4” on one side and plain on the other side.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

ETORICOXIB CIPLA film-coated tablets are indicated for:

- 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

##### Rheumatoid arthritis (RA)

The recommended dose is 90 mg once per day. In some patients, 60 mg once daily may provide adequate therapeutic benefit.

**Ankylosing spondylitis (AS)**

The recommended dose is 90 mg once per day. In some patients, 60 mg once daily may provide adequate therapeutic benefit.

**Short-term relief of acute pain**

The recommended dose is 90 or 120 mg once per day. The treatment period must not exceed 8 days.

**Acute gouty arthritis**

The recommended dose is 120 mg once per day. The treatment period must not exceed 8 days.

**Primary dysmenorrhoea**

The recommended dose is 120 mg once per day.

**Post-operative dental pain**

The recommended dose is 90 mg once per day.

There are no data to support doses higher than those recommended for the indication.

Therefore:

The dose for Rheumatoid Arthritis (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 post-operative acute dental surgery pain should not exceed 90 mg daily.

**DO NOT EXCEED THE RECOMMENDED DOSES.**

The risk of cardiovascular adverse events is increased with the higher doses and prolonged treatment periods. Therefore, the lowest effective dose should be used for the shortest treatment duration possible. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically (see **section 4.4**).

## **Special populations**

### **Elderly**

No dose adjustments are required for patients older than 65 years of age. Although the elderly may be more susceptible to renal, gastrointestinal and cardiovascular adverse events (see **section 4.4** and **4.8**). When using ETORICOXIB CIPLA 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 CIPLA

**Hepatic dysfunction**

A once daily dose of 60 mg should not be exceeded in patients with mild hepatic impairment (Child-Pugh score 5 to 6).

Doses should be reduced in patients with moderate hepatic impairment (Child-Pugh score 7 - 9). The recommended dose of 60 mg every other day should not be exceeded.

There are no data to support use in patients with severe hepatic impairment (Child-Pugh higher than 9). ETORICOXIB CIPLA is contraindicated in these patients (see **section 4.3** and **5.0**).

**Renal impairment**

No dose adjustments are required in patients with mild to moderate renal impairment (creatinine clearance  $\geq$  30 mL/min). ETORICOXIB CIPLA is contraindicated in patients with creatinine clearance less than 30 mL/min (see **section 4.3**).

**Paediatric population**

The safety and efficacy of ETORICOXIB CIPLA in children has not yet been established

**Method of administration**

ETORICOXIB CIPLA is administered orally. It may be taken with or without food. Use the lowest effective dose for the shortest possible duration of treatment.

**4.3 Contraindications**

**ETORICOXIB CIPLA** film-coated tablets are contraindicated in:

- Patients with known hypersensitivity to etoricoxib or any of the other ingredients of ETORICOXIB CIPLA
- Patients with active peptic ulceration or gastrointestinal (GI) bleeding
- Patients with severe hepatic insufficiency (Child-Pugh score greater than 9 or serum albumin less than 25 g/L)
- Patients with estimated creatinine clearance of less than 30 mL/min
- Patients who have developed signs of asthma, acute rhinitis, nasal polyps, angioedema or urticaria following administration of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) including ETORICOXIB CIPLA
- Uncontrolled hypertension
- Pregnancy and lactation (see **section 4.6**)
- 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 (see **section 4.4**)
- Peri-operative analgesia in the setting of coronary artery bypass surgery (CABG)
- Patients who are receiving concomitant lithium therapy with ETORICOXIB CIPLA as this increases plasma levels of lithium (see **section 4.5**)
- Patients who are at high risk of digoxin toxicity as concomitant use of ETORICOXIB CIPLA with digoxin may increase  $C_{max}$  of digoxin by approximately 33 %.

#### 4.4 Special warnings and precautions for use

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

Risk of renal tubular acidosis and hypokalaemia are associated with non-steroidal anti-inflammatory medicine (NSAID) usage.

### **Hypersensitivity reactions**

Serious skin reactions (such as exfoliative dermatitis, Steven-Johnson syndrome and toxic epidermal necrolysis) which may be fatal can occur. Serious hypersensitivity reactions like anaphylaxis and angioedema have been reported (see **section 4.8**).

There is a high risk of skin reactions in patients with a history of allergies. Treatment should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of allergy.

### **Cardiovascular effects**

Caution is advised when ETORICOXIB CIPLA is prescribed to patients with cardiovascular risk factors such as hypertension, diabetes, smoking and hypercholesterolaemia.

Due to inhibition of prostaglandin synthesis, fluid retention and oedema have been observed in patients taking ETORICOXIB CIPLA, therefore ETORICOXIB CIPLA 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 NSAIDs like ETORICOXIB CIPLA can be associated with new onset or recurrent congestive heart failure. Therefore, ETORICOXIB CIPLA must be used with caution in patients with a history of heart diseases, left ventricular dysfunction or hypertension or in patients with pre-existing

oedema from any other reason. Should the conditions of these patients exacerbate further, appropriate measures including discontinuation of treatment should be taken.

ETORICOXIB CIPLA may cause more frequent and severe hypertension than other NSAIDs and COX-2 inhibitors. Therefore, blood pressure monitoring is advised during treatment with ETORICOXIB CIPLA. If blood pressure increases significantly, alternative treatments should be considered.

The selective COX-2 inhibitor class of medicines, to which ETORICOXIB CIPLA belongs, is associated with a high risk of thrombotic events, especially myocardial infarction and stroke. Prolonged treatment periods and high doses increase the risk of cardiovascular events. Therefore, the lowest effective doses and shortest treatment periods possible should be used during treatment with ETORICOXIB CIPLA. The patient's need for symptomatic relief and response to therapy must be assessed periodically.

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with ETORICOXIB CIPLA after careful consideration.

### **Gastrointestinal effects**

ETORICOXIB CIPLA can cause upper gastrointestinal complications such as perforations, ulcers or bleeding (PUBs), some of which may be fatal. Caution should be exercised during administration in patients with high risk factors such as patients using any other NSAIDs (including aspirin) concurrently, or those with pre-existing gastrointestinal complications

[perforations, ulcers or bleeding (PUBS) and the elderly]. Concurrent use with aspirin, even at low doses, carries a high risk of gastrointestinal events like ulceration and bleeding.

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

Caution is advised when treatment is initiated in patients with dehydration. Rehydration should occur prior to initiating ETORICOXIB CIPLA treatment in dehydrated patients.

Because of its lack of platelet effect, ETORICOXIB CIPLA is not a substitute for aspirin in cardiovascular prophylaxis. Because ETORICOXIB CIPLA does not inhibit platelet aggregation, anti-platelet therapies should not be discontinued, but should be considered in patients with increased risk factors or with a history of cardiovascular or thrombotic events. There is no evidence to suggest that concurrent use with aspirin alleviates the increased risk of serious cardiovascular thrombotic events (see **section 4.5**).

Extreme caution is advised and appropriate medical monitoring should occur during treatment in the elderly and in patients with cardiac, hepatic or renal impairment. If conditions of these patients are aggravated during ETORICOXIB CIPLA therapy, appropriate measures including discontinuation of treatment, should occur.

Long-term administration of NSAIDs such as ETORICOXIB CIPLA may result in renal papillary necrosis and other renal injury. Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion. Therefore, under conditions of compromised renal perfusion, administration of ETORICOXIB CIPLA may cause a reduction in prostaglandin formation and secondarily, in renal blood flow and thereby impairing renal function. Patients who have significantly impaired pre-existing renal function, uncompensated heart failure or liver cirrhosis

are at great risk of developing impaired renal function. Monitoring of renal and hepatic function in such patients is required.

Elevations of alanine aminotransferase (ALT) and 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 up to one year with ETORICOXIB CIPLA 60 mg and 90 mg daily.

Patients with signs of liver dysfunction or abnormal liver function tests should be evaluated for abnormal liver enzyme activity regularly. Treatment should be discontinued if abnormal liver function tests (3 times the upper limit of normal) are observed.

ETORICOXIB CIPLA may mask fever or other symptoms of inflammation or infections.

### **Lactose**

ETORICOXIB CIPLA film-coated tablets contain lactose. Patients with the rare hereditary problems of galactose intolerance total lactase deficiency or glucose-galactose malabsorption should not take ETORICOXIB CIPLA.

## **4.5 Interaction with other medicinal products and other forms of interaction**

### **Ciclosporin and tacrolimus**

Concurrent use of ETORICOXIB CIPLA or any other NSAID can cause nephrotoxicity due to ciclosporin or tacrolimus. Renal function should be monitored when ETORICOXIB CIPLA is co-administered with ciclosporin or tacrolimus.

**Warfarin**

ETORICOXIB CIPLA daily doses of 120 mg in patients that were on warfarin treatment were associated with approximately 13 % increases in prothrombin time International Normalised Ratio (INR). INR values should be monitored periodically during co-administration with warfarin or similar medicines.

**Rifampicin**

Rifampicin has been reported to reduce etoricoxib exposure by 65 % due to its role in induction of hepatic metabolism. This effect should be considered prior to its simultaneous use with ETORICOXIB CIPLA.

**Methotrexate**

Doses of ETORICOXIB CIPLA 120 mg have been reported to increase methotrexate exposure (AUC) by 28 % and reduce renal clearance by 13 %. The risk of methotrexate toxicity should be taken into account when high doses (above 90 mg per day) of ETORICOXIB CIPLA is administered concomitantly with methotrexate.

**Diuretics, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)**

Non-selective NSAIDs and COX-2 inhibitors such as ETORICOXIB CIPLA have been reported to reduce the antihypertensive effects of diuretics.

Concurrent use of ETORICOXIB CIPLA with ACE inhibitors or ARBs in patients with compromised renal function (such as the elderly or volume depleted patients including those on diuretic therapy) can exacerbate renal function further or even lead to acute renal failure, which may be reversible. Caution is advised during co-administration, especially in the elderly or in patients with renal insufficiency. Patients should be hydrated properly prior to initiation of therapy. Renal function should be monitored at the start and during therapy.

### **Lithium**

ETORICOXIB CIPLA may increase lithium plasma levels. This interaction should be taken into account during their co-administration.

### **Aspirin**

Once daily doses (120 mg) of ETORICOXIB CIPLA do not have an effect on the anti-platelet activity of aspirin (81 mg per day). ETORICOXIB CIPLA may be used concomitantly with aspirin at dosage levels (or low doses) used for cardiovascular prophylaxis. However, simultaneous use even at this level increases the risk of gastrointestinal complications (ulcers and bleeding) when compared to when ETORICOXIB CIPLA is used alone. Therefore, simultaneous intake of aspirin at levels above doses used for cardiovascular prophylaxis is not recommended (see **section 4.4**).

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

### **Oral contraceptives**

ETORICOXIB CIPLA must be given with care when used in women on oral contraceptive therapy, particularly those taking ethinyl oestradiol (EE). Doses of ETORICOXIB CIPLA (at 60 and 120 mg) given with EE 35 µg and 0,5 to 1 mg norethindrone (NET) raised the steady state of EE AUC<sub>(0-24)</sub> by 37 % and 50 - 60 %, respectively, with no clinically relevant effect on NET. Raised EE levels may increase the incidence of adverse events (such as venous thromboembolic events) in women.

### **Furosemide**

ETORICOXIB CIPLA decreases natriuretic and antihypertensive effects of furosemide and thiazides. This effect has been attributed to inhibition of renal prostaglandin synthesis.

### **Hormone replacement therapy (HRT)**

ETORICOXIB CIPLA doses of 120 mg administered together with HRT consisting of 0,625 mg conjugated oestrogens for 28 days increased mean steady state AUC<sub>(0-24h)</sub> of unconjugated oestrone by 41 %, equilin by 76 % and 17-beta-oestradiol by 22 %. The effects of ETORICOXIB CIPLA 120 mg on the exposure (AUC<sub>(0-24h)</sub>) 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 are unknown, and higher doses of conjugated oestrogens were not studied in combination with ETORICOXIB CIPLA. These interactions must be considered when prescribing ETORICOXIB CIPLA to women taking HRT as the extended oestrogen exposure increases the risk of oestrogen-related adverse events.

**Antivirals**

Concomitant use of NSAIDs such as ETORICOXIB CIPLA with zidovudine increases the risk of haematotoxicity.

Ritonavir can raise NSAIDs', such as ETORICOXIB CIPLA 's, plasma concentrations, thereby increasing the incidence of ETORICOXIB CIPLA -related adverse events.

**Effects on medicines metabolised by sulfotransferases**

ETORICOXIB CIPLA inhibits human sulfotransferases, particularly SULT1E1 and it has been demonstrated to raise plasma concentrations of ethinyl oestradiol. Prescribers should exercise caution when using ETORICOXIB CIPLA together with other medicines metabolised by human sulfotransferases such as oral salbutamol and minoxidil.

There have been reports of a 33 % increase in digoxin  $C_{max}$  levels in healthy volunteers (see **section 4.3**).

**Other**

Use of more than one NSAID together should be avoided because of the risk of adverse events.

The risk of gastrointestinal bleeding and ulceration associated with NSAIDs is increased when used with corticosteroids, selective serotonin reuptake inhibitors (SSRIs), venlafaxine, anti-platelets (clopidogrel and ticlopidine), iloprost, erlotinib, sibutramine, alcohol, bisphosphonates or pentoxifylline.

#### **4.6 Fertility, pregnancy and lactation**

##### **Women of childbearing potential / Contraception in males and females**

ETORICOXIB CIPLA is not recommended in fertile women trying to conceive.

##### **Pregnancy**

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

No clinical data is available on exposed pregnancies for etoricoxib. Animal studies have shown reproductive toxicity. The potential for human risk in pregnancy is unknown. Etoricoxib, as with other medicinal products inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester.

#### **4.7 Effects on ability to drive and use machines**

Dizziness, asthenia and blurred vision may occur. Patients who experience these side effects should exercise caution as these side effects can impair the ability to drive and operate machinery.

#### **4.8 Undesirable effects**

##### **Infections and infestation**

*Frequent:* Alveolar osteitis.

*Less frequent:* Gastroenteritis, upper respiratory tract infection, urinary tract infection.

### **Blood and lymphatic system disorders**

*Less frequent:* Anaemia (primarily associated with gastrointestinal bleeding), leukopenia.

*Frequency unknown:* Thrombocytopenia.

### **Metabolism and nutrition disorders**

*Frequent:* Oedema or fluid retention.

*Less frequent:* Increased or decreased appetite, weight gain.

### **Psychiatric disorders**

*Less frequent:* Anxiety, mental acuity decreased.

*Frequency unknown:* Confusion, hallucinations, depression, restlessness.

### **Nervous system disorders**

*Frequent:* Dizziness, headache.

*Less frequent:* Insomnia, paraesthesia / hypoesthesia, aseptic meningitis.

*Frequency unknown:* Dysgeusia, somnolence, cerebrovascular incidents (strokes).

### **Eye disorders**

*Less frequent:* Conjunctivitis.

*Frequency Unknown:* Blurred vision, photosensitivity.

### **Ear and labyrinth disorders**

*Less frequent:* Tinnitus, vertigo.

### **Cardiac disorders**

*Frequent:* Palpitations.

*Less frequent:* Congestive cardiac failure, myocardial infarction, cardiovascular thrombotic events, atrial fibrillation, angina, non-specific ECG changes.

*Frequency unknown:* Dysrhythmia, tachycardia, aggravated hypertension.

### **Vascular disorders**

*Frequent:* Hypertension.

*Less frequent:* Flushing, transient ischaemic attack, peripheral oedema, vasculitis.

*Frequency unknown:* Hypertensive crisis, aggravated hypertension.

### **Respiratory, thoracic and mediastinal disorders**

*Less frequent:* Cough, dyspnoea, epistaxis.

*Frequency unknown:* Bronchospasm.

### **Gastrointestinal disorders**

*Frequent:* Gastrointestinal complications (such as abdominal pain, flatulence and/or heartburn), diarrhoea, dyspepsia, epigastric discomfort, nausea.

*Less frequent:* Abdominal distension, acid reflux, bowel movement pattern change, constipation, dry mouth, gastro-duodenal ulcer, irritable bowel syndrome, oral ulcer, vomiting, gastritis pancreatitis.

*Frequency unknown:* Peptic ulcers including gastrointestinal perforation, and bleeding (mostly in the elderly).

### **Skin and subcutaneous tissue disorders**

*Frequent:* Ecchymosis.

*Less frequent:* Facial oedema, pruritus, rash, erythema.

*Frequency unknown:* Steven-Johnson syndrome, toxic epidermal necrolysis, urticaria, fixed drug eruption.

### **Musculoskeletal, connective tissue and bone disorders**

*Less frequent:* Muscular cramps or spasms, musculoskeletal pain, stiffness.

### **Renal and urinary system disorders**

*Less frequent:* Proteinuria.

*Frequency unknown:* Renal insufficiency including renal failure (see **section 5.2**), nephrotoxicity including interstitial nephritis and nephrotic syndrome.

**Hepato-biliary disorders**

*Frequency unknown:* Hepatitis, jaundice, hepatic failure, hepatotoxicity including pancreatitis.

**General disorders and administrative site conditions**

*Frequent:* Asthenia / fatigue, flu-like disease.

*Less frequent:* Chest pain.

**Immune system disorders**

*Frequency unknown:* Hypersensitivity reactions including angioedema, anaphylactic/anaphylactoid reactions including shock.

**Investigations**

*Frequent:* Raised liver enzyme activity (ALT and AST).

*Less frequent:* Blood urea increased, creatinine phosphokinase increased, haematocrit decreased, haemoglobin decreased, hyperkalaemia, leukocytes decreased, platelets decreased, serum creatinine increased, uric acid increased, blood sodium decreased.

**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> or to Cipla Medpro (Pty) Ltd at [drugsafetysa@cipla.com](mailto:drugsafetysa@cipla.com) or telephone 080 222 6662 (toll free).

#### **4.9 Overdose**

The most frequent signs of overdosage include gastrointestinal complications and renovascular adverse events.

In the event of overdosage, the usual supportive measures should be employed. The unabsorbed material should be removed from the gut, patients should be clinically monitored and if necessary, supportive therapy should be given.

Haemodialysis is not effective in ETORICOXIB CIPLA overdosage treatment, and it is not known whether peritoneal dialysis is effective.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: A 3.1 Anti-rheumatics (anti-inflammatory agents).

ATC code: M01 AH05

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

## 5.2 Pharmacokinetic properties

### ***Absorption***

After oral administration, etoricoxib is absorbed with a mean oral bioavailability of approximately 100 %. Etoricoxib peak plasma concentration (geometric mean  $C_{max}$ ) of 3,6 µg/mL was observed after approximately 1 hour ( $t_{max}$ ) when 120 mg daily doses were administered to adults under fasted conditions. The pharmacokinetics of etoricoxib are linear over clinical dose range.

Food (a standard meal) did not have a significant clinical effect on the extent or rate of absorption of etoricoxib when 120 mg doses were administered.

No major differences in pharmacokinetics were observed when etoricoxib was administered with or without antacids in healthy adults (40 - 65 years of age), namely, magnesium / aluminium hydroxide or calcium carbonate (approximately 50 mEq acid neutralising capacity) as the AUC was found to be comparable while  $C_{max}$  was well within 20 %.

### ***Distribution***

Etoricoxib plasma protein binding is approximately 92 % over concentrations of 0,05 to 5 µg/mL in humans. At steady state, the volume of distribution ( $V_{dss}$ ) is approximately 120 L.

Etoricoxib crosses the placenta and the blood-brain barrier.

### ***Biotransformation***

Etoricoxib undergoes hepatic metabolism predominantly, with less than 1 % of the dose recovered in the urine as the parent drug. Five metabolites have been identified in humans.

Etoricoxib is mainly metabolised by cytochrome P450 enzymes to form the 6'-hydroxymethyl derivative which undergoes oxidation to form the principal metabolite 6'-carboxylic acid

derivative. The major metabolites either have no measurable activity or act as weak inhibitors of COX-2.

### ***Elimination***

Following a 25 mg single dose intravenous administration of radio-labelled etoricoxib, 70 % radioactivity was recovered in the urine and 20 % in the faeces, mainly as metabolites. Afterwards, plasma and urine were collected for 7 days while stool was collected for 10 days. Less than 2 % was recovered as unchanged drug.

Elimination of etoricoxib is almost exclusively through metabolism followed by renal excretion. Steady state concentrations are reached after 7 days of once daily administrations of 120 mg, with an accumulation ratio of approximately 2, which is nearly equivalent to an accumulation half-life of approximately 22 hours. The plasma clearance is approximately 50 mL/min.

### ***Pharmacokinetics in special populations***

#### ***Elderly***

In elderly patients (65 years and older) with normal renal function, no pharmacokinetic differences were observed. However, the incidence of adverse events was higher in the elderly.

#### ***Patients with hepatic impairment***

Etoricoxib exposure (AUC) was approximately 16 % higher in patients with mild hepatic impairment (Child-Pugh score 5 to 6) when compared to healthy patients that received the same treatment regimen of 60 mg once daily for 21 days.

Patients with moderate hepatic impairment (Child-Pugh score greater than 9) administered with etoricoxib 60 mg on every other day for 21 days showed similar exposure (AUC) to healthy patients that were administered with daily doses of 60 mg for 21 days.

No data are available in patients with severe hepatic impairment (Child-Pugh score 7 to 9) (see **section 4.3** and **4.2**).

#### *Patients with renal impairment*

No significant pharmacokinetic differences were observed when a single dose of etoricoxib 120 mg was administered to patients with moderate (creatinine clearance 30 to 50 mL/min) to severe (creatinine clearance less than 30 mL/min) renal insufficiency or in patients with end-stage renal disease on haemodialysis. Haemodialysis contributed negligibly to elimination (dialysis clearance approximately 50 mL/min).

#### *Paediatrics*

Etoricoxib has not been studied in patients under 12 years of age. Safety and efficacy of ETORICOXIB CIPLA have not been established in paediatric and adolescent patients.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### **Core Tablet**

Anhydrous calcium hydrogen phosphate

Croscarmellose sodium

Magnesium stearate

Microcrystalline cellulose

**Film coated Tablet**

Opadry II white 39K580004 (ETORICOXIB CIPLA 60)

Opadry II green 39K510004 (ETORICOXIB CIPLA 90 and ETORICOXIB CIPLA 120)

**Composition of the film-coat (Opadry)**

Hypromellose 15 mPas (E464)

Hypromellose 50 mPas (E464)

Lactose monohydrate

Titanium dioxide (E171)

Triacetin

\*Iron Oxide yellow (E172)

\*Indigo carmine (E132)

\* Only applicable for ETORICOXIB CIPLA 90 and ETORICOXIB CIPLA 120

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

24 months

#### **6.4 Special precautions for storage**

Store at or below 30 °C. Store in the original package. Keep well closed.

#### **6.5 Nature and contents of container**

ETORICOXIB CIPLA film-coated tablets are packed in:

- Packs of 7's in Alu/Alu blisters that are placed into an outer cardboard carton.
- Packs of 10's in Alu/Alu blisters that are placed into an outer cardboard carton.
- Packs of 30's in Alu/Alu blisters that are placed into an outer cardboard carton or in white HDPE bottles fitted with white child-resistant caps embossed with the instruction "TO OPEN PUSH DOWN AND TURN & CLOSE TIGHTLY". The 30's HDPE packs contain a 2 g silica gel desiccant.
- Packs of 90's in white HDPE bottles fitted with white child-resistant caps embossed with the instruction "TO OPEN PUSH DOWN AND TURN & CLOSE TIGHTLY". The 90's HDPE packs contain a 1 g silica gel desiccant.
- The silica gel desiccant is made from a non-woven fabric bag and heat sealed along the edges with the manufacturer's details printed in blue ink.

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**

**CIPLA MEDPRO (PTY) LTD.**

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

**8. REGISTRATION NUMBER(S)**

ETORICOXIB CIPLA 60: 50/3.1/0813

ETORICOXIB CIPLA 90: 50/3.1/0814

ETORICOXIB CIPLA 120: 50/3.1/0815

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

09 June 2020

**10. DATE OF REVISION OF THE TEXT**

13 July 2023