Professional Information for AZCURA 60, 90 & 120

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

AZCURA 60 film-coated tablets

AZCURA 90 film-coated tablets

AZCURA 120 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AZCURA 60: Each film-coated tablet contains 60 mg etoricoxib.

AZCURA 90: Each film-coated tablet contains 90 mg etoricoxib.

AZCURA 120: Each film-coated tablet contains 120 mg etoricoxib.

AZCURA 60: Contains sugar (1 mg lactose monohydrate).

AZCURA 90: Contains sugar (1,5 mg lactose monohydrate).

AZCURA 120: Contains sugar (2 mg lactose monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

AZCURA 60: Light green to bluish-green, round, biconvex, film-coated tablets debossed ‘60’ on one side and plain on the other side. The tablet should be free of all physical defects.

AZCURA 90: White to off-white, round, biconvex, film-coated tablets debossed ‘90’ on one side and plain on the other side. The tablet should be free of all physical defects.

AZCURA 120: Green, round, biconvex, film-coated tablets debossed '120' on one side and plain on the other side. The tablet should be free of all physical defects.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AZCURA is indicated for the:

- 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 AZCURA 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

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

Rheumatoid arthritis (RA)

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

Ankylosing spondylitis (AS)

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 or 120 mg once daily, limited to a maximum of 8 days treatment.

Acute gouty arthritis

The recommended dose is 120 mg once daily. AZCURA 120 should be used only for the acute symptomatic period, 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 RA should not exceed 90 mg daily.

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

The dose for acute gouty arthritis 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.

As the cardiovascular risks of AZCURA may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically (see section 4.4).

Elderly

No dosage adjustment of AZCURA is necessary for elderly patients although the elderly may be

susceptible to renal, gastrointestinal and cardiovascular adverse effects (see section 4.4).
When using AZCURA 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.

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.

Renal insufficiency

No dosage adjustment is necessary for patients with a creatinine clearance ≥ 30 mL/min. The use of AZCURA in patients with creatinine clearance < 30 mL/min is contraindicated (see section 4.3).

Method of administration

AZCURA is administered orally and may be taken with or without food.

4.3 Contraindications

- Known hypersensitivity to etoricoxib or to any of the inactive ingredients of AZCURA (see section 4.3).
- Patients with a history of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including AZCURA.
- Patients with active or history of recurrent ulcer, haemorrhage or perforations.
- Patients with active peptic ulceration or active gastrointestinal (GI) bleeding.
- Patients with severe hepatic dysfunction (Child-Pugh score > 9 or serum albumin < 25 g/L).

- Patients with severe renal impairment (estimated creatinine clearance < 30 mL/min).
- Patients who have developed signs of asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria following the administration of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) including AZCURA.
- Hypertension which has not been adequately controlled.
- Pregnancy and lactation (see section 4.6).
- Children and adolescents under the age of 16 years.
- 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).
- Perioperative analgesia in the setting of coronary artery bypass surgery (CABG).
- Lithium therapy: Concomitant administration with AZCURA may lead to toxic blood concentration 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).

4.4 Special warnings and precautions for use

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

Gastrointestinal effects

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

Caution is advised with treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs such as AZCURA: the elderly, patients using any other NSAID or aspirin concomitantly, or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.

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

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

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

AZCURA should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn’s disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated.

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

Cardiovascular effects

AZCURA may be associated with a risk of thrombotic events (especially myocardial infarction and stroke). As the cardiovascular risks of AZCURA 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 required in patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus or smoking) and should only be treated with AZCURA after careful consideration (see section 5.1).

AZCURA is not a substitute for aspirin for prophylaxis of cardiovascular thromboembolic diseases because of their lack of antiplatelet effect. Antiplatelet therapies should therefore not be discontinued (see sections 4.5 and 5.1).

Renal effects

Long-term use of NSAIDs such as AZCURA has led to 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 AZCURA may cause a reduction in prostaglandin formation and secondarily, in renal blood flow, and thereby impair renal function. Patients at greatest risk of this response are those with pre-existing significantly impaired renal function, uncompensated heart failure or cirrhosis. Monitoring of renal function in such patients should be considered.

Fluid retention, oedema and hypertension

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

Fluid retention, oedema and hypertension have been observed in patients taking AZCURA. AZCURA can be associated with new onset or recurrent congestive heart failure. For information regarding a dose related response for etoricoxib see section 5.1.

Caution is required in patients with a history of hypertension and/or heart failure, as fluid retention and oedema have been reported in association with AZCURA therapy. In view of the AZCURA's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

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

Hepatic effects

Elevations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (approximately three or more times the upper limit of normal) have been reported in approximately 1 % of patients in clinical trials treated for up to one year with AZCURA 60 mg and 90 mg daily. Any patients with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be monitored. AZCURA should be discontinued if signs of hepatic insufficiency occur, or if persistently abnormal liver function tests (three times the upper limit of normal) are detected.

Skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have very rarely been reported in association with the use of NSAIDs and selective COX-2 inhibitors such as AZCURA during post-marketing surveillance (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy, with the onset of the reaction occurring in the majority of cases within the first month of treatment. Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been

reported in patients receiving AZCURA (see section 4.8). Some selective COX-2 inhibitors such as AZCURA have been associated with an increased risk of skin reactions in patients with a history of any medicine allergy.

AZCURA should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in patients taking NSAIDs such as AZCURA. 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. Eosinophilia 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 AZCURA and evaluate the patient immediately.

General

AZCURA may mask fever and other signs of inflammation.

Caution should be exercised when coadministering AZCURA with warfarin or other oral anticoagulants (see section 4.5).

The use of AZCURA, as with any medicine known to inhibit cyclooxygenase or prostaglandin synthesis, is not recommended in women attempting to conceive (see sections 4.6, 5.1 and 5.3).

When using AZCURA 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.

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

AZCURA contains lactose monohydrate

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take AZCURA.

AZCURA contains sodium

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

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

Oral anticoagulants

Patients receiving oral anticoagulants should be closely monitored for their prothrombin time (INR), particularly in the first few days when therapy with AZCURA is initiated or the dose of AZCURA is changed (see section 4.4).

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

Increased risk of gastrointestinal bleeding.

Diuretics, ACE inhibitors and angiotensin receptor blockers

AZCURA may reduce the antihypertensive effect of diuretics, ACE inhibitors and angiotensin

receptor blockers. This interaction should be given consideration in patients taking AZCURA concomitantly with these medicines.

In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the coadministration of an ACE inhibitor or angiotensin receptor blocker may result in further deterioration of renal function, including possible acute renal failure, which may be reversible. These interactions should be considered in patients taking AZCURA concomitantly with ACE inhibitors or angiotensin receptor blockers. 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.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

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

Aspirin

AZCURA can be used concomitantly with aspirin at doses used for cardiovascular prophylaxis (low-dose aspirin). However, concomitant administration of low-dose aspirin with AZCURA may result in an increased rate of GI ulceration or other complications compared to use of AZCURA alone. Concomitant administration of AZCURA with doses of aspirin above those for cardiovascular prophylaxis or with other NSAIDs is not recommended (see sections 4.4 and 5.1).
Because of its lack of platelet effects, AZCURA is not a substitute for aspirin for cardiovascular prophylaxis.
There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with AZCURA.

Ciclosporin and tacrolimus

Although this interaction has not been studied with AZCURA, coadministration of ciclosporin or tacrolimus with any NSAID such as AZCURA, may increase the nephrotoxic effect of ciclosporin or tacrolimus. Renal function should be monitored when AZCURA and either of these medicines is used in combination.

Pharmacokinetic interactions

The effect of AZCURA on the pharmacokinetics of other medicines

Lithium

NSAIDs such as AZCURA and selective COX-2 inhibitors decrease lithium renal excretion and therefore increase plasma lithium levels. This interaction should be given consideration in patients taking AZCURA concomitantly with lithium (see section 4.3).

Methotrexate

AZCURA 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 AZCURA at dosages > 90 mg daily and methotrexate are administered concomitantly.

Oral contraceptives

AZCURA is an inhibitor of human sulfotransferase activity and has been shown to increase the plasma concentration of ethinylestradiol (EE).

This increase in EE concentration should be considered when selecting an oral contraceptive for the use with AZCURA. An increase in EE exposure can increase the incidence of side effects associated with oral contraceptives (e.g. venous thrombo-embolic events in women at risk).

Hormone replacement therapy (HRT)

The effects of AZCURA 120 on the exposure (AUC_{0-24h}) to conjugated oestrogens were less than half of those observed when conjugated oestrogen 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 AZCURA. These increases in oestrogenic concentration should be taken into consideration when selecting post-menopausal hormone therapy for the use with AZCURA because the increase in oestrogen exposure might increase the risk of side effects associated with HRT.

Prednisone or prednisolone

AZCURA did not have clinically important effects on the pharmacokinetics of prednisone or prednisolone.

The risk of GI perforation, bleeding and ulceration (PUBs) is increased when AZCURA is taken with corticosteroids.

Digoxin

AZCURA 120 did not alter the steady-state plasma AUC_{0-24h} or renal elimination of digoxin. There was an increase in digoxin C_{max} (approximately 33 %) in health volunteers. Patients should be monitored when AZCURA and digoxin are administered concomitantly (see section 4.3).

Effect of AZCURA on medicines metabolised by sulfotransferases

AZCURA is an inhibitor of human sulfotransferase activity and has been shown to increase the serum concentrations of ethinylestradiol. Take special care when administering AZCURA concurrently with other medicines primarily metabolised by human sulfotransferases (e.g. oral salbutamol and minoxidil).

Ketoconazole

Ketoconazole, a potent inhibitor of CYP3A4, did not have any clinically important effect on the

single-dose pharmacokinetics of 60 mg AZCURA (43 % increase in AUC).

Voriconazole and miconazole

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

Rifampicin

Coadministration of AZCURA with rifampicin, a potent inducer of CYP enzymes, produced a 65 % decrease in AZCURA plasma concentrations. This interaction may result in recurrence of symptoms when AZCURA is coadministered with rifampicin. While this information may suggest an increase in dose, doses of AZCURA greater than those listed for each indication, have not been studied in combination with rifampicin and are therefore not recommended (see section 4.2).

Antacids

Antacids do not affect the pharmacokinetics of AZCURA to a clinically relevant extent.

Furosemide

AZCURA may reduce the natriuretic effect of furosemide and thiazides.

4.6 Fertility, pregnancy and lactation

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

Pregnancy

The use of NSAIDs, including AZCURA around 20 weeks gestation or later, in pregnancy may cause a rare but serious foetal renal dysfunction, leading to oligohydramnios and, in some cases, neonatal renal impairment. Complications of prolonged oligohydramnios include limb contractures

and delayed lung maturation, which may require invasive procedures such as exchange transfusion or dialysis, in some cases.

Etoricoxib may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester, persistent pulmonary hypertension of the newborn and delay in the onset of labour. If a woman becomes pregnant during treatment, AZCURA must be discontinued.

Regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) during the third trimester of pregnancy, may result in premature closure of the fetal ductus arteriosus *in utero*, and possibly, in persistent pulmonary hypertension of the newborn. The onset of labour may be delayed, and its duration increased.

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

Breastfeeding

It is not known whether etoricoxib is excreted in human milk. Etoricoxib is excreted in the milk of lactating rats. Safety in human lactation has not been established. Women who use AZCURA must not breast feed (see sections 4.3 and 5.3).

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Infections and infestations

Frequent: Alveolar osteitis

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

Blood and lymphatic system disorders

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

Immune system disorders

Less frequent: Hypersensitivity reactions, including angioedema, anaphylactic/anaphylactoid reactions including shock

Metabolism and nutrition disorders

Frequent: Oedema/fluid retention

Less frequent: Appetite increase or decrease, weight gain

Psychiatric disorders

Less frequent: Anxiety, depression, decreased mental acuity, confusion, restlessness, hallucinations

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, non-specific ECG changes, myocardial infarction, angina pectoris

Vascular disorders

Frequent: Hypertension

Less frequent: Flushing, cerebrovascular accident*, transient ischemic attack, hypertensive crisis, vasculitis

*AZCURA has been associated with an increased risk of serious thrombotic arterial events, including myocardial infarction and stroke.

Respiratory, thoracic and mediastinal disorders

Frequent: Bronchospasm

Less frequent: Coughing, dyspnoea, epistaxis

Gastrointestinal disorders

Frequent: Abdominal pain, constipation, flatulence, gastritis, heartburn, acid reflux, diarrhoea, dyspepsia, epigastric discomfort, nausea, vomiting, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, oesophagitis, oral ulcer

Less frequent: Abdominal distention, bowel movement pattern change, dry mouth, gastroduodenal ulcer, irritable bowel syndrome, peptic ulcers including

gastrointestinal perforation and bleeding (mainly in the elderly), pancreatitis

Hepatobiliary disorders

Frequent: Increased ALT, increased AST

Less frequent: Hepatitis, jaundice, hepatic failure

Skin and subcutaneous tissue disorders

Frequent: Ecchymosis

Less frequent: Facial oedema, pruritus, rash, erythema, urticaria, bullous reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, fixed drug eruption

Frequency unknown: Drug reaction with eosinophilia 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, renal insufficiency (see section 4.4), including renal failure or increased serum creatinine

General disorders and administration site conditions

Frequent: Asthenia, fatigue, flu-like symptoms

Less frequent: Chest pain

Investigations

Less frequent: Increased blood urea nitrogen, increased creatine phosphokinase, decreased haematocrit, decreased haemoglobin, hyperkalaemia, decreased leukocytes,

decreased platelets, increased uric acid, decreased blood sodium.

The following serious side effects have been reported in association with the use of NSAIDs and cannot be ruled out for AZCURA: nephrotoxicity including interstitial nephritis and nephrotic syndrome.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of AZCURA is important. It allows continued monitoring of the benefit/risk balance of AZCURA. Health care providers are requested to report any suspected adverse drug reactions via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

The most frequently observed side effects were GI events and renovascular events. In the event of suspected 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.

AZCURA is not dialysable by haemodialysis. It is not known whether AZCURA is dialysable by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Pharmacotherapeutic group: Antiinflammatory and antirheumatic products, nonsteroids, coxibs,

ATC code: MO1 AH05.

Etoricoxib is a nonsteroidal 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

Etoricoxib is well absorbed from the gastrointestinal tract after oral doses. The absolute bioavailability is approximately 100 %. Following a 120 mg once daily dosing to steady state, the peak plasma concentration (geometric mean C_{max} equal to 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_{0-24h}) was 37,8 µg/h/mL. The pharmacokinetics of etoricoxib is linear across the clinical dose range.

Dosing with food (a high-fat meal) had no effect on the extent of absorption of etoricoxib after administration of a 120 mg dose.

Distribution

Etoricoxib is approximately 92 % bound to 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 with less than 1 % of a dose recovered in urine as the parent drug. The major route of metabolism is via cytochrome P450 isoenzymes including CYP3A4 to form the 6'-hydroxymethyl derivative of etoricoxib, which is then oxidised to the 6’-carboxylic acid derivative, the major metabolite. Both are inactive or only weak cyclo-oxygenase -2 (COX-2) inhibitors. Five metabolites have been identified in man.

Elimination

Elimination of etoricoxib occurs almost exclusively through metabolism followed by renal excretion. At steady state the half-life of etoricoxib is about 22 hours. The plasma clearance after a 25 mg intravenous dose is estimated to be approximately 50 mL/min.

Pharmacokinetics in special patient groups

Elderly patients: Pharmacokinetics in the elderly (65 years of age and older) are similar to adults. In reported clinical studies, a higher incidence of adverse events was experienced in older patients compared to younger patients.

Gender: The pharmacokinetics of etoricoxib is similar between men and women.

Hepatic insufficiency: Patients with mild hepatic dysfunction (Child-Pugh score 5 to 6) who were 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 dysfunction (Child-Pugh score 7 to 9) who were administered etoricoxib 60 mg every other day, had similar mean AUC compared to the healthy subjects given etoricoxib 60 mg once daily for 21 days. There are no clinical or pharmacokinetic data in patients with severe hepatic dysfunction (Child-Pugh score > 9) (see sections 4.2 and 4.3).

Renal insufficiency: The pharmacokinetics of a single dose of 120 mg etoricoxib in patients with moderate to severe renal insufficiency and patients with end-stage renal disease on haemodialysis were not significantly different from those in healthy subjects. Haemodialysis contributed negligibly to elimination (dialysis clearance approximately 50 mL/min) (see sections 4.3 and 4.4).

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium laurilsulfate

Microcrystalline cellulose (E460)

Low-substituted hydroxypropyl cellulose (E463)

Anhydrous calcium hydrogen phosphate (E341)

Croscarmellose sodium (E468)

Anhydrous colloidal silica (E551)

Magnesium stearate (E572)

Instacoat Universal Green (for AZCURA 60 and AZCURA 120)

Instacoat Universal White (for AZCURA 90)

Lactose monohydrate

Glycerol triacetate (E1518).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister strip in the outer carton until required for use.

6.5 Nature and contents of container

Silver aluminium/aluminium blister strips containing 7 tablets per blister strip.

Pack sizes:

AZCURA 60: 28 tablets packed into a cardboard box.

AZCURA 90 and 120: 7 or 28 tablets packed into a cardboard box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building B, Ground Floor

22 Karee Street

Centurion, Pretoria

0157

Tel: 012 748 6400

8. REGISTRATION NUMBERS

AZCURA 60: 47/3.1/0546

AZCURA 90: 47/3.1/0547

AZCURA 120: 47/3.1/0548

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

30 June 2020

10. DATE OF REVISION OF THE TEXT

24 February 2026