1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

MARACOXA 60 (film-coated tablet)

MARACOXA 90 (film-coated tablet)

MARACOXA 120 (film-coated tablet)

2 QUALITIVE AND QUANTITIVE COMPOSITION

MARACOXA 60:

Each film-coated tablet contains 50 mg of etoricoxib.

Excipient(s) with known effect:

Contains sugar (lactose monohydrate) 1,680 mg

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

For full list of excipients, see section 6.1.

MARACOXA 90:

Each film-coated tablet contains 90 mg of etoricoxib.

Excipient(s) with known effect:

Contains sugar (lactose monohydrate) 2,520 mg

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

For full list of excipients, see section 6.1.

MARACOXA 120:

Each film-coated tablet contains 120 mg of etoricoxib.

Excipient(s) with known effect:

Contains sugar (lactose monohydrate) 3,360 mg

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

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

MARACOXA 60:

A green film-coated, round, biconvex, bevelled edge tablet debossed with “E” on one side and “60” on the other side.

MARACOXA 90:

A white film-coated, round, biconvex, bevelled edge tablet debossed with “E” on one side and “90” on the other side.

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MARACOXA 120:

A pale green film-coated, round, biconvex, bevelled edge tablet debossed with “E” on one side and “120” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MARACOXA 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 dysmenorrhea.
- Treatment of moderate to severe acute post-operative pain associated with dental surgery.

The decision to prescribe a selective COX-2 inhibitor, such as MARACOXA, 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

MARACOXA is administered orally.

MARACOXA may be taken with or without food.

MARACOXA should be administered for the shortest duration possible and the lowest effective daily dose should be used.

- **Osteo-arthritis (OA):**

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The recommended dose is 60 mg once daily.

- **Rheumatoid arthritis (RA):**

The recommended dose is 90 mg once daily.

- **Ankylosing spondylitis:**

The recommended dose is 90 mg once daily.

- **Short-term relief of acute pain:**

The recommended dose is 90 mg or 120 mg once daily, limited to a maximum of 8 days treatment.

- **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 post-operative acute dental surgery pain should not exceed 90 mg

daily.

As the cardiovascular risks of selective COX-2 inhibitors, as in MARACOXA 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 MARACOXA is necessary for the elderly or based on gender or race. Although the elderly may be more susceptible to renal, gastrointestinal and cardiovascular side effects *(see section 4.4 and 4.8).*

When using MARACOXA 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.

Clinical experience is limited particularly in patients with moderate dysfunction and caution

is advised. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score greater than 9), therefore its use is contraindicated in these patients (*see section 4.3 and 5.2*).

Renal insufficiency:

No dosage adjustment is necessary for patients with lesser degrees of renal insufficiency (creatinine clearance greater than or equal to 30 ml/min). The use of etoricoxib, as in MARACOXA, in patients with creatinine clearance less than 30 ml/min is contraindicated *(see section 4.3)*.

Method of administration

For oral use.

4.3 Contraindications

MARACOXA is contraindicated in:

- Patients with known hypersensitivity to etoricoxib or any of the excipients of MARACOXA.
- Patients with active peptic ulceration or gastro-intestinal (GI) bleeding.
- Patients with severe hepatic dysfunction (Child-Pugh score greater than 9 or serum albumin less than 25 g/ℓ).
- Patients with estimated creatinine clearance less than 30 ml/min.
- Patients who have developed signs of asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria following the administration of aspirin or other non-steroidal anti-inflammatory medicines (NSAIMs) including COX-2 inhibitors.
- Hypertension which has not been adequately controlled.

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- Pregnancy and lactation.
- Children and adolescents under 16 years of age.
- Patients with inflammatory bowel disease.
- Patients with congestive heart failure (NYHA II-IV).
- Established ischaemic heart disease, 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 MARACOXA may lead to toxic blood concentration of lithium *(see section 4.5*).
- Digoxin: There was an increase in digoxin Cmax (approximately 33 %) in healthy volunteers (*see section 4.5)*.

4.4 Special warnings and precautions for use

MARACOXA may predispose to cardiovascular events, gastro-intestinal events or cutaneous reactions which may be fatal.

Renal effects

Long-term administration of NSAIDs, such as MARACOXA, 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 MARACOXA 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.

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

Severe hypokalaemia and renal tubular acidosis have been reported due to prolonged use of NSAIDs at higher than recommended doses. This risk is increased with the use of codeine/ NSAIDs as patients may become dependent on the codeine component. Presenting signs and symptoms included reduced level of consciousness and generalised weakness. NSAIDs induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

Opioid use disorder with codeine/ NSAIDs combinations (abuse and dependence)

Codeine is a narcotic analgesic. No more than the stated dose of this medicine should be taken. Tolerance, physical and psychological dependence and opioid use disorder (OUD) may develop upon repeated administration of opioids such as codeine. Abuse or intentional misuse of codeine/ NSAIDs combinations may result in overdose and/or death.

Serious clinical outcomes, including fatalities, have been reported in association with abuse and dependence with codeine/ NSAIDs combinations, particularly when taken for prolonged periods at higher than recommended doses. These have included reports of gastrointestinal perforations, gastrointestinal haemorrhages, severe anaemia, renal failure, renal tubular acidosis and severe hypokalaemia associated with the NSAIDs component.

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Patients should be informed about the risks and signs of opioid use disorder (OUD) with the use of codeine in codeine/ NSAIDs combinations, as well as serious clinical outcomes. If these signs occur, patients should be advised to contact their doctor.

Withdrawal symptoms, such as restlessness and irritability may occur once the codeine/ NSAIDs combinations is stopped.

Fluid retention, oedema and hypertension

Fluid retention, oedema and hypertension have been observed in patients taking etoricoxib, as in MARACOXA. All non-steroidal anti-inflammatory medicines (NSAIDs), including MARACOXA, 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 MARACOXA should be taken. MARACOXA may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors. Therefore, special attention should be paid to blood pressure monitoring during treatment with MARACOXA. If blood pressure rises significantly, alternative treatment should be considered.

Cardiovascular effects

Clinical trials suggest that the selective COX-2 inhibitor class of medicines, such as MARACOXA, may be associated with an increased risk of thrombotic events (especially MI and stroke). As the cardiovascular risks of selective COX-2 inhibitors, such as MARACOXA, 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 and hypercholesterolaemia) should only be treated with MARACOXA after careful consideration.

MARACOXA is not a substitute for aspirin for cardiovascular prophylaxis because of its lack of effect on platelets. Because etoricoxib, as in MARACOXA, does not inhibit platelet aggregation, antiplatelet therapies should not be discontinued and if indicated should be considered in patients at risk for or with a history of cardiovascular or other thrombotic events. There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with etoricoxib, as in MARACOXA *(see section 4.5)*.

General

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 NSAIDs and some selective COX-2 inhibitors, such as MARACOXA during post-marketing surveillance *(see section 4.8)*. These serious events may occur without warning. Patients appear to be at highest risk for these reactions early in the course of therapy: 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 etoricoxib, as in MARACOXA *(see section 4.8)*. Some selective COX-2 inhibitors, such as MARACOXA have been associated with an increased risk of skin reactions in patients with a history of any medicine allergy. MARACOXA should

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

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

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

When using MARACOXA 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.

Gastro-intestinal effects

Upper gastro-intestinal complications (perforations, ulcers or bleedings (PUBs)), some of them resulting in fatal outcome, have occurred in patients treated with etoricoxib, as in MARACOXA.

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

There is a further increase in risk of gastro-intestinal adverse effects (gastro-intestinal ulceration or other gastro-intestinal complications) when etoricoxib, as in MARACOXA, is taken concomitantly with aspirin (acetylsalicylic acid) (even at low doses).

Hepatic effects

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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 etoricoxib 60 mg and 90 mg daily.

A 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 (three times the upper limit of normal) are detected, MARACOXA should be discontinued.

Lactose warning

MARACOXA tablets contain lactose in each tablet (1,680 mg, 2,520 mg and 3,350 mg in the 60-, 90-, and 120-mg tablets, respectively), which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patient with hereditary problems of galactose intolerance, e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take MARACOXA.

Sodium

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

4.5 Interaction with other medicines and other forms of Interaction

Ciclosporin and tacrolimus:

Although this interaction has not been studied with etoricoxib, co-administration of ciclosporin or tacrolimus with any NSAID may increase the nephrotoxic effect of ciclosporin

or tacrolimus. Renal function should be monitored when MARACOXA and either of these medicines is used in combination.

Warfarin:

In patients stabilised on chronic warfarin therapy, the administration of etoricoxib as contained in MARACOXA 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 MARACOXA is initiated or changed in patients receiving warfarin or similar medicines.

Rifampicin:

Co-administration of etoricoxib such as MARACOXA 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 MARACOXA is co-administered with rifampicin.

Methotrexate:

Two studies investigated the effects of etoricoxib 60 mg, 90 mg or 120 mg administered once daily for seven 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. In one 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 etoricoxib, as in MARACOXA, at doses greater than 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 may diminish the antihypertensive effect of diuretics, ACE inhibitors and ARBs. This interaction should be given consideration in patients taking MARACOXA concomitantly with these medicines.

In some patients with compromised renal function (e.g. elderly patients or patients who are volume depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory medicines, including selective COX-2 inhibitors, 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 renal function at initiation of concomitant administration and periodically thereafter.

Lithium:

Reports suggest that NSAIDs and selective COX-2 inhibitors such as MARACOXA may increase plasma lithium levels *(see section 4.3)*.

Aspirin:

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In a 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).
MARACOXA can be used concomitantly with aspirin at doses used for cardiovascular prophylaxis (low-dose aspirin). However, concomitant administration of low-dose aspirin with etoricoxib, as in MARACOXA, increases the rate of GI ulceration or other complications compared to use of etoricoxib alone. Concomitant administration of etoricoxib, as in MARACOXA, with doses of aspirin above those for cardiovascular prophylaxis or with other NSAIDs should be avoided *(see section 4.4).*

Oral contraceptives:

Etoricoxib 60 mg given concomitantly with an oral contraceptive containing 35 mcg ethinyl estradiol (EE) and 0,5 mg to 1 mg norethindrone for 21 days increased the steady state AUC0-24hr of EE by 37 %. Etoricoxib 120 mg given with the same oral contraceptive concomitantly or separated by 12 hours increased the steady state AUC0-24hr of EE by 50 % to 60 %. This increase in EE concentration should be considered when selecting an oral contraceptive for use with etoricoxib, as in MARACOXA. An increase in EE exposure can increase the incidence of adverse events associated with oral contraceptives (e.g. venous thrombo embolic events in women at risk).

Furosemide:

Clinical studies have shown that NSAIDs such as etoricoxib reduce the natriuretic effect of furosemide and thiazides in patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Hormone replacement therapy:

1.3.1.1 Professional Information for medicines for human use

Administration of etoricoxib 120 mg with hormone replacement therapy consisting of conjugated oestrogens (0,625 mg for 28 days, increased the mean steady state AUC0-24hr of unconjugated oestrone (41 %), equilin (76 %), and 17-beta-estradiol (22 %). The effect of the recommended chronic doses of MARACOXA, (60 mg and 90 mg), has not been studied. The effects of etoricoxib 120 mg on the exposure (AUC0-24hr) to these oestrogenic components of conjugated oestrogens were less than half of those observed when conjugated oestrogens was administered alone and the dose was increased from 0,625 mg to 1,25 mg. The clinical significance of these increases is unknown, and higher doses of conjugated oestrogens were not studied in combination with etoricoxib.
These increases in oestrogenic concentration should be taken into consideration when selecting post-menopausal hormone therapy for use with etoricoxib, as in MARACOXA, because the increase in oestrogen exposure might increase the risk of adverse events associated with Hormone Replacement Therapy (HRT).

Effects of MARACOXA 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 estradiol. While knowledge about effects of multiple sulfotransferases is presently limited and the clinical consequences for many medicines are still being examined, it may be prudent to exercise care when administering etoricoxib, as in MARACOXA, concurrently with other medicines primarily metabolised by human sulfotransferases (e.g. oral salbutamol and minoxidil).

Digoxin:

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Etoricoxib 120 mg administered once daily for 10 days to healthy volunteers did not alter the steady plasma AUC0-24 hr or renal elimination of digoxin. There was an increase in digoxin Cmax (approximately 33 %) *(see section 4.3)*.

Other:

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

Antacids did not have clinically important effects on the pharmacokinetics of etoricoxib.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

The potential for human risk in pregnancy is unknown. Etoricoxib may cause uterine inertia and premature closure of the ducts arteriosus during the last trimester. If a woman becomes pregnant during treatment, MARACOXA must be discontinued.

Breastfeeding

Mothers on MARACOXA should not breastfeed their infants.

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4.7 Effects on ability to drive and use machines

No studies on the effect of etoricoxib on the ability to drive or use machines have been performed. However, patients who experience dizziness, vertigo or somnolence while taking MARACOXA should refrain from driving or operating machinery.

4.8 Undesirable effects

Tabulated list of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequent	Alveolar osteitis
	Less frequent	Gastro-enteritis, upper respiratory infection, urinary tract infection
Blood and lymphatic system disorders	Less frequent	Anaemia, leucopenia
	Frequency unknown	Thrombocytopenia
Immune system disorders	Frequency unknown	Hypersensitivity reactions, including angioedema, anaphylactic/anaphylactoid reactions including shock
Metabolism and nutrition disorders	Frequent	Oedema/fluid retention
	Less frequent	Increased or decreased appetite, weight gain
	Frequency	Hypokalaemia*

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MedDRA system organ class	**Frequency**	**Adverse reactions**
	not known	
Psychiatric disorders	Less frequent	Anxiety, depression, decreased mental acuity
	Frequency unknown	Restlessness, confusion, hallucinations
Nervous system disorders	Frequent	Dizziness, headache
	Less frequent	Dysgeusia, insomnia, paresthesia/hypaesthesia
	Frequency unknown	Somnolence, cerebrovascular incidents (stroke)
Eye disorders	Less frequent	Conjunctivitis
	Frequency unknown	Blurred vision
Ear and labyrinth disorders	Less frequent	Tinnitus, vertigo
Cardiac disorders	Frequent	Palpitations
	Less frequent	Atrial fibrillation, congestive heart failure, non-specific ECG changes, myocardial infarction, angina
	Frequency unknown	Dysrhythmia and tachycardia
Vascular disorders	Frequent	Hypertension
	Less frequent	Flushing, transient ischaemic attack, vasculitis

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MedDRA system organ class	Frequency	Adverse reactions
	Frequency unknown	Hypertensive crisis, aggravated hypertension
Respiratory, thoracic and mediastinal disorders	Less frequent	Cough, dyspnoea, epistaxis
	Frequency unknown	Bronchospasm
Gastrointestinal disorders	Frequent	Gastro-intestinal disorders (e.g. abdominal pain, flatulence, heartburn), diarrhoea, dyspepsia, epigastric discomfort, nausea
	Less frequent	Abdominal distension, acid reflux, bowel movement pattern change, constipation, dry mouth, gastroduodenal ulcer, irritable bowel syndrome, oesophagitis, oral ulcer, vomiting, gastritis, pancreatitis
	Frequency unknown	Peptic ulcers including gastro-intestinal perforation and bleeding (mainly in the elderly)
Hepato-biliary disorders	Frequency unknown	Hepatitis, jaundice, hepatic failure
Skin and subcutaneous tissue disorders	Frequent	Ecchymosis
	Less frequent	Facial oedema, pruritus, rash, erythema, urticaria
	Frequency unknown	Stevens-Johnson syndrome, toxic epidermal necrolysis, fixed medicine

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MedDRA system organ class	Frequency	Adverse reactions
		eruption
Musculoskeletal and connective tissue disorders	Less frequent	Muscular cramp/spasm, musculoskeletal pain/stiffness
Renal and urinary disorders	Less frequent	Proteinuria
	Frequency unknown	Renal insufficiency, including renal failure, nephrotoxicity including interstitial nephritis and nephrotic syndrome
	Not known	Renal tubular acidosis*
General disorders and administration site conditions	Frequent	Asthenia/fatigue, flu-like disease
	Less frequent	Chest pain
Investigations	Frequent	Increased ALT; increased AST
	Less frequent	Increased blood urea, increased creatine phosphokinase, decreased haematocrit, decreased haemoglobin, hyperkalaemia, decreased leukocytes, decreased platelets, increased serum creatinine, increased uric acid, decreased blood sodium

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Description of selected adverse reactions

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

*Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of the NSAIDs component at higher than recommended doses due to dependence on the codeine component.

Reporting of suspected adverse reactions

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

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (*see section 4.8)*.

The most frequently observed adverse experiences were consistent with the safety profile for etoricoxib (e.g. gastro-intestinal events, renovascular events).

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (*see section 4.4 and section 4.8).*

Treatment should be symptomatic and supportive.

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In the event of overdose, it is reasonable to employ the usual supportive measures, e.g. remove unabsorbed material from the gastro-intestinal 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

PHARMACOLOGICAL CLASSIFICATION:

A 3.1 Anti-rheumatics (Anti-inflammatory agents)

Pharmacotherapeutic group and ATC code:

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

5.2 Pharmacokinetic properties

Absorption:

Orally administered etoricoxib is well absorbed. The mean oral bioavailability is approximately 100 %.

Following 120 mg once-daily dosing to steady state, the peak plasma concentration (geometric mean Cmax = 3,6 mcg/ml) was observed at approximately 1 hour (Tmax) after administration to fasted adults. The geometric mean AUC0-24hr was 37,8 mcg/hr/ml. The pharmacokinetics of etoricoxib is linear across the clinical dose range.

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A standard meal had no clinically meaningful effect on the extent or rate of absorption of a dose of etoricoxib 120 mg. In clinical trials, etoricoxib was administered without regard to food.

The pharmacokinetics of etoricoxib in 12 healthy subjects were similar (comparable AUC, Cmax within approximately 20 %) when administered alone, with a magnesium/aluminium hydroxide antacid or a calcium carbonate antacid (approximately 50 mEq acid-neutralising capacity).

Distribution:

Etoricoxib is approximately 92 % bound to human plasma protein over the range of concentrations of 0,05 mcg/ml to 5 mcg/ml. The volume of distribution at steady state (Vdss) is approximately 120 ℓ in humans.

Etoricoxib crosses the placenta and the blood-brain barrier.

Biotransformation:

Etoricoxib is extensively metabolised in the liver with less than 1 % of a dose recovered in urine as the parent compound. The major route of metabolism to form the 6'-hydroxymethyl derivative is catalysed by cytochrome P450 (CYP) enzymes.

Five metabolites have been identified in man. The principal metabolite is the 6'-carboxylic acid derivatives of etoricoxib formed by further oxidation of the 6'-hydroxymethyl

derivatives. These principal metabolites either demonstrate no measurable activity or are only weakly active as COX-2 inhibitors. None of these metabolites inhibit COX-1.

Elimination:

Following administration of a single 25 mg radiolabelled intravenous dose of etoricoxib to healthy subjects, 70 % of radioactivity was recovered in urine and 20 % in faeces, mostly as metabolites. Less than 2 % was recovered unchanged.

Elimination of etoricoxib occurs almost exclusively through metabolism followed by renal excretion. Steady state concentrations of etoricoxib are reached within seven days of once-daily administration of 120 mg, with an accumulation ratio of approximately 2, corresponding to an accumulation half-life of approximately 22 hours. The plasma clearance is estimated to be approximately 50 ml/min.

Characteristics in patients:

Elderly:

Pharmacokinetics in the elderly (65 years of age and older) with normal renal function are similar to those in the young. No dosage adjustment is necessary for elderly patients (*see section 4.2.).* In 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 had similar mean AUC to the healthy subjects given etoricoxib 60 mg once daily. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score greater than 9) (*see section 4.3 and 4.2: Hepatic insufficiency.)*

Renal insufficiency:

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

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

Paediatric patients:

The pharmacokinetics of etoricoxib in paediatric patients (less than 12 years of age) have not been studied. In a pharmacokinetic study (N = 16) conducted 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 greater than 60 kg 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

MARACOXA 60:

Core: calcium hydrogen phosphate anhydrous, cellulose microcrystalline, croscarmellose sodium (Ac-Di-Sol), magnesium stearate, silica colloidal anhydrous, {coating: Opadry II

green 31K510020 (composition: HPMC hypromellose (15cP), lactose monohydrate, titanium dioxide, triacetin, iron oxide yellow, FD&C blue #2/indigo carmine aluminium lake (dye strength (11 %-14 %), carnuba wax)}.

MARACOXA 90:

Core: calcium hydrogen phosphate anhydrous, cellulose microcrystalline, croscarmellose sodium (Ac-Di-Sol), magnesium stearate, silica colloidal anhydrous, {coating: Opadry II white 31K580000 (composition: HPMC hypromellose (15cP), lactose monohydrate, titanium dioxide, triacetin, carnuba wax)}.

MARACOXA 120:

Core: calcium hydrogen phosphate anhydrous, cellulose microcrystalline, croscarmellose sodium (Ac-Di-Sol), magnesium stearate, silica colloidal anhydrous, {coating: Opadry II green 31K510019 (composition: HPMC hypromellose (15cP), lactose monohydrate, titanium dioxide, triacetin, FD&C blue #2/indigo carmine, aluminium lake (dye strength (3 %-5 %), iron oxide yellow, carnuba wax)}

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

1.3.1.1 Professional Information for medicines for human use

Blisters: Store in the original package in order to protect from moisture and keep in the carton until required for use.

Bottles: Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Cold form blister pack comprises of cold form laminate (aluminium foil laminated to oriented polyamide on one side and laminated to PVC on other side i.e. OPA/Al/PVC) on one side and hard tempered aluminum foil (coated with VMCH heat seal lacquer) on the other side. Suitable number of blister strips will be placed in an outer cardboard carton. The number of tablets per strip and the number of strips in carton shall be based on commercial requirement.

PVC/PVdC blister pack comprises of clear, transparent PVC laminated with PVdC on one side and hard tempered aluminium foil coated with heat seal lacquer on other side (PVdC/PVC/Al). Heat seal lacquer contains 86 % Vinyl Chloride, 13 % Vinyl Acetate & 1 % maleic acid.

Suitable number of blister strips will be placed in an outer cardboard carton. The number of tablets per strip and the number of strips in each carton shall be based on commercial requirement.

HDPE bottle pack comprises of round wide mouth white high-density polyethylene (HDPE) bottle with white opaque polypropylene (PP) screw closure with induction sealing liner along with wad.

1.3.1.1 Professional Information for medicines for human use

The HDPE bottle pack may either be placed in an outer cardboard carton or provided without a carton based on commercial requirement.

Pack sizes:

60 mg: 28’s, 30’s

90 mg: 7’s, 28’s, 30’s

120 mg: 7’s, 28’s, 30’s

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

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

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Viatris South Africa (Pty) Ltd

4 Brewery Street

Isando

Johannesburg, 1600

Republic of South Africa

8 REGISTRATION NUMBER(S)

MARACOXA 60: 49/3.1/0588

MARACOXA 90: 49/3.1/0589

MARACOXA 120: 49/3.1/0590

1.3.1.1 Professional Information for medicines for human use

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 May 2020

10 DATE OF REVISION OF TEXT

16 January 2024