Approved Professional Information for Medicines for Human Use

ETORICOXIB 30 mg AUSTELL

ETORICOXIB 60 mg AUSTELL

ETORICOXIB 90 mg AUSTELL

ETORICOXIB 120 mg AUSTELL

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ETORICOXIB 30 mg AUSTELL

ETORICOXIB 60 mg AUSTELL

ETORICOXIB 90 mg AUSTELL

ETORICOXIB 120 mg AUSTELL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ETORICOXIB 30 mg AUSTELL film-coated tablet contains 30 mg etoricoxib.

Each ETORICOXIB 60 mg AUSTELL film-coated tablet contains 60 mg etoricoxib.

Each ETORICOXIB 90 mg AUSTELL film-coated tablet contains 90 mg etoricoxib.

Each ETORICOXIB 120 mg AUSTELL film-coated tablet contains 120 mg etoricoxib.

Contains sugar (lactose monohydrate).

Each ETORICOXIB 30 mg AUSTELL film-coated tablet contains 2,52 mg lactose monohydrate.

Each ETORICOXIB 60 mg AUSTELL film-coated tablet contains 5,04 mg lactose monohydrate.

Each ETORICOXIB 90 mg AUSTELL film-coated tablet contains 7,56 mg lactose

monohydrate.

Each ETORICOXIB 120 mg AUSTELL film-coated tablet contains 10,08 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets (tablets).

ETORICOXIB 30 mg AUSTELL: Blue-green, apple-shaped, biconvex film-coated tablets engraved ‘30’ on one face with the other face plain.

ETORICOXIB 60 mg AUSTELL: Dark-green, apple-shaped, biconvex film-coated tablets engraved ‘60’ on one face with the other face plain.

ETORICOXIB 90 mg AUSTELL: White, apple-shaped, biconvex film-coated tablets engraved ‘90’ on one face with the other face plain.

ETORICOXIB 120 mg AUSTELL: Pale-green, apple-shaped, biconvex film-coated tablets engraved ‘120’ on one face with the other face plain.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ETORICOXIB AUSTELL is indicated for the:

- Symptomatic relief of osteoarthritis (OA) and rheumatoid arthritis (RA)
- Treatment of ankylosing spondylitis (AS)
- Treatment of acute gouty arthritis
- Short-term relief of acute pain, treatment limited to a maximum period of 8 days
- Treatment of primary dysmenorrhoea
- Treatment of moderate to severe acute post-operative pain associated with dental surgery.

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks (see section 4.4).

4.2 Posology and method of administration

Posology

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

Osteoarthritis (OA)

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

Rheumatoid arthritis (RA)

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

Ankylosing spondylitis (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, 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 AS 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 ETORICOXIB AUSTELL 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 population

No dosage adjustment of ETORICOXIB AUSTELL is necessary for the elderly, although the elderly may be more susceptible to renal, gastrointestinal and cardiovascular side effects (see sections 4.4 and 4.8).

Hepatic impairment

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 and administration of 30 mg once daily can also be considered.

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

Renal impairment

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 AUSTELL in patients with creatinine clearance less than 30 mL/min is contraindicated (see section 4.3).

Paediatric population

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

Method of administration

ETORICOXIB AUSTELL is administered orally and may be taken with or without food. The onset of the effect of the medicine may be faster when ETORICOXIB AUSTELL is administered without food. This should be considered when rapid symptomatic relief is needed.

4.3 Contraindications

ETORICOXIB AUSTELL is contraindicated in the following:

- known hypersensitivity to etoricoxib or to any of the excipients of ETORICOXIB AUSTELL listed in section 6.1
- patients who have developed signs of asthma, acute rhinitis, nasal polyps, angioedema or urticaria following the administration of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) including COX-2 inhibitors such as ETORICOXIB AUSTELL
- active peptic ulceration or gastrointestinal (GI) bleeding
- severe hepatic dysfunction (Child-Pugh score greater than 9 or serum albumin less than 25 g/L)
- severe renal impairment (estimated creatinine clearance less than 30 mL/min)
- uncontrolled hypertension
- pregnancy and lactation (see sections 4.4 and 4.6)
- children and adolescents under 16 years of age
- inflammatory bowel disease
- 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 ETORICOXIB AUSTELL may lead to toxic blood concentrations of lithium (see section 4.5)
- digoxin: there was an approximate increase of 33 % in digoxin C_{max} in healthy volunteers (see section 4.5).

4.4 Special warnings and precautions for use

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

Gastrointestinal effects

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

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

There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) when ETORICOXIB AUSTELL is taken concomitantly with aspirin (acetylsalicylic acid) (even at low doses). It is reported that a significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid vs. NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials.

Cardiovascular effects

It is reported that clinical trials suggest that the selective COX-2 inhibitor class of drugs may be associated with a risk of thrombotic events (especially myocardial infarction (MI) and stroke), relative to placebo and some NSAIDs. As the cardiovascular risks of etoricoxib as in ETORICOXIB AUSTELL 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, especially in patients with osteoarthritis (see sections 4.2, 4.3 and 4.8).

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

COX-2 selective inhibitors, such as ETORICOXIB AUSTELL, are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effect. Therefore, antiplatelet therapies should not be discontinued (see sections above, 4.5 and 5.1). There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic event associated with ETORICOXIB AUSTELL (see section 4.5).

Renal effects

Administration of NSAIDs such as ETORICOXIB AUSTELL over long periods of time has resulted in renal injuries including renal papillary necrosis.

Renal blood flow is maintained by prostaglandins in the presence of renal vasoconstriction. Under conditions of compromised renal perfusion, the administration of ETORICOXIB AUSTELL may cause a reduction in prostaglandin formation and hence a decrease in the compensatory maintenance of renal perfusion by prostaglandins resulting in impairment of renal function. Patients at greatest risk of this response are those with pre-existing significantly impaired renal function, uncompensated heart failure or cirrhosis. In such patients, monitoring of renal and hepatic function should be considered.

Caution is recommended when initiating treatment with ETORICOXIB AUSTELL in patients with dehydration. It is advisable to rehydrate patients prior to starting therapy with ETORICOXIB AUSTELL.

Risk of foetal renal dysfunction and premature closure of foetal ductus arteriosus

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) 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 may include limb contractures and delayed lung maturation (see sections 4.3 and 4.6), which may require invasive procedures such as exchange transfusion or dialysis in some cases.

These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation.

Oligohydramnios is often, but not always, reversible following the discontinuation of an NSAID and reappeared after re-initiation of treatment.

The use of NSAIDS in pregnant women at 20 weeks or later in pregnancy must be avoided due to the risk of foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment.

If NSAID treatment is deemed necessary between 20 to 30 weeks of pregnancy, limit use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if NSAID treatment extends beyond 48 hours. Discontinue the NSAID if oligohydramnios occurs and follow up according to clinical practice (see sections 4.3 and 4.6).

Because of the additional risk of premature closure of the foetal ductus arteriosus, the prescribing of NSAIDs at 30 weeks and later in pregnancy must be avoided (see section 4.6).

Fluid retention, oedema and hypertension

As with other medicines known to inhibit prostaglandin synthesis, fluid retention, oedema and hypertension have been observed in patients taking etoricoxib as in ETORICOXIB AUSTELL. All Nonsteroidal Anti-inflammatory Drugs (NSAIDs), including etoricoxib, can be associated with new onset or recurrent congestive heart failure (see section 4.8). 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 etoricoxib should be taken.

Etoricoxib as in ETORICOXIB AUSTELL 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 ETORICOXIB AUSTELL (see section 4.3) and special attention should be paid to blood pressure monitoring during treatment with ETORICOXIB AUSTELL. Blood pressure should be monitored within two weeks after initiation of treatment and periodically thereafter. 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 etoricoxib 30, 60 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. If signs of hepatic insufficiency occur, or if persistently abnormal liver function tests (three times the upper limit of normal) are detected, ETORICOXIB AUSTELL should be discontinued.

Skin reactions

Serious skin reactions, which may be fatal, may occur. Exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported less frequently in association with the use of NSAIDs and some selective COX-2 inhibitors during post-marketing surveillance and may occur without warning (see section 4.8). The highest risk for these reactions appears to be 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 ETORICOXIB AUSTELL (see section 4.8). An increased risk of skin reactions in patients with a history of any drug allergy has been observed with some selective COX-2 inhibitors such as ETORICOXIB AUSTELL.

At the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity, therapy with ETORICOXIB AUSTELL should be discontinued.

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 ETORICOXIB AUSTELL. 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 ETORICOXIB AUSTELL and evaluate the patient immediately.

General

If during treatment, patients deteriorate in any of the organ system functions described above, appropriate measures should be taken and discontinuation of etoricoxib therapy should be considered. Medically appropriate supervision should

be maintained when using ETORICOXIB AUSTELL in the elderly and in patients with renal, hepatic, or cardiac dysfunction.

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

ETORICOXIB AUSTELL may mask fever and other signs of inflammation or infection.

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

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

Excipient: lactose

ETORICOXIB AUSTELL tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

Oral anticoagulants

In subjects stabilised on chronic warfarin therapy, concurrent administration of etoricoxib 120 mg daily was associated with an approximate 13 % increase in

prothrombin time International Normalized Ratio (INR). Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with ETORICOXIB AUSTELL is initiated or the dose of ETORICOXIB AUSTELL is changed (see section 4.4).

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

The antihypertensive effect of diuretics, ACE inhibitors and ARBs may be diminished during use of non-selective NSAIDs and COX-2 selective inhibitors such as ETORICOXIB AUSTELL. This interaction should be given consideration in patients taking ETORICOXIB AUSTELL 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) a further deterioration of renal function including possible acute renal failure may result when undergoing treatment with selective COX-2 inhibitors such as ETORICOXIB AUSTELL, and concurrent administration of ACE inhibitors or ARBs. These effects may be reversible. Caution is advised when the combination is used, especially in the elderly.

Aspirin (acetylsalicylic acid)

It has been reported that 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). Because of its lack of antiplatelet effect, ETORICOXIB AUSTELL is not a substitute for aspirin for cardiovascular prophylaxis. Doses of aspirin used for cardiovascular prophylaxis (low-dose aspirin) may be used concurrently with ETORICOXIB AUSTELL. However, concomitant administration of low-dose aspirin with ETORICOXIB AUSTELL may result in an increased rate of GI ulceration or other complications compared to use of ETORICOXIB AUSTELL alone. Concomitant

administration of ETORICOXIB AUSTELL with aspirin at doses *exceeding* those for cardiovascular prophylaxis or with other NSAIDs is not recommended (see section 4.4).

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

Ciclosporin and tacrolimus

Co-administration of ciclosporin or tacrolimus with any NSAID, such as ETORICOXIB AUSTELL**,** may increase the nephrotoxic effect of these medicines. When ETORICOXIB AUSTELL and either of these medicines is used concurrently, monitoring of renal function is advised.

Pharmacokinetic interactions

Effect of etoricoxib on the pharmacokinetics of other medicines

Lithium

NSAIDs and selective COX-2 inhibitors such as ETORICOXIB AUSTELL decrease lithium renal excretion and therefore increase plasma lithium levels. This interaction should be considered in patients taking ETORICOXIB AUSTELL concomitantly with lithium (see section 4.3). If necessary, monitor blood lithium closely and adjust the lithium dosage while the combination is being taken and when the NSAID is withdrawn.

Methotrexate

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 has been investigated in two studies. Etoricoxib at 60 mg and 90 mg had no effect on methotrexate plasma concentrations (as measured by AUC)

or renal clearance. Etoricoxib 120 mg had no effect on methotrexate plasma concentration (as measured by AUC) or renal clearance in one study and in the other, a 28 % increase of methotrexate plasma concentration (as measured by AUC) and 13 % reduction of renal clearance of methotrexate was observed. When ETORICOXIB AUSTELL at doses greater than 90 mg daily and methotrexate are administered concomitantly, monitoring for methotrexate-related toxicity is recommended.

Oral contraceptives

When etoricoxib 60 mg was given concomitantly with an oral contraceptive containing 35 µg ethinyl estradiol (EE) and 0,5 mg to 1 mg norethindrone for 21 days, steady state $AUC_{0\text{-}24hr}$ of EE increased by 37 %. Etoricoxib 120 mg given with the same oral contraceptive concomitantly or separated by 12 hours, increased the steady state $AUC_{0\text{-}24hr}$ of EE by 50 to 60 %. When selecting an oral contraceptive for use with ETORICOXIB AUSTELL this increase in EE concentration should be considered. 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

A reduction of the natriuretic effect of furosemide and thiazides with the use of NSAIDs such as ETORICOXIB AUSTELL has been observed in clinical studies. This response has been attributed to inhibition of renal prostaglandin synthesis.

Hormone Replacement Therapy (HRT)

Administration of etoricoxib 120 mg with hormone replacement therapy consisting of conjugated oestrogens (0,625 mg) for 28 days, increased the mean steady state

$AUC_{0\text{-}24hr}$ of unconjugated estrone (41 %), equilin (76 %), and 17-beta-estradiol (22 %). The effect of the recommended chronic doses of ETORICOXIB AUSTELL (30 mg, 60 mg and 90 mg) has not been studied. The effects of etoricoxib 120 mg on the exposure ($AUC_{0\text{-}24hr}$) 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 AUSTELL because the increase in oestrogen exposure might increase the risk of adverse events associated with Hormone Replacement Therapy (HRT).

Prednisone/prednisolone

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

Digoxin

The steady-state plasma $AUC_{0\text{-}24hr}$ or renal elimination of digoxin was not altered by co-administration of etoricoxib 120 mg once daily for 10 days in healthy volunteers. There was an increase in digoxin C_{max} (approximately 33 %), see section 4.3. This increase is not generally important for most patients. However, patients at high risk of digoxin toxicity should be monitored for this when etoricoxib and digoxin are administered concomitantly.

Effect of etoricoxib on medicines metabolised by sulfotransferases

ETORICOXIB AUSTELL 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 AUSTELL concurrently with other medicines primarily metabolised by these enzymes (such as oral salbutamol and minoxidil).

Effect of etoricoxib on medicines metabolised by CYP isoenzymes

Based on *in vitro* studies, etoricoxib is not expected to inhibit cytochromes P450 (CYP) 1A2, 2C9, 2C19, 2D6, 2E1 or 3A4. In a study in healthy subjects, daily administration of etoricoxib 120 mg did not alter hepatic CYP3A4 activity as assessed by the erythromycin breath test.

Effects of other medicines on the pharmacokinetics of etoricoxib

The main pathway of etoricoxib metabolism is dependent on CYP enzymes. CYP3A4 appears to contribute to the metabolism of etoricoxib *in vivo. In vitro* studies indicate that CYP2D6, CYP2C9, CYP1A2 and CYP2C19 also can catalyse the main metabolic pathway, but their quantitative roles have not been studied *in vivo*.

Ketoconazole

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

Voriconazole and miconazole

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

Rifampicin

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

Antacids

Antacids do not affect the pharmacokinetics of etoricoxib as in ETORICOXIB AUSTELL to a clinically relevant extent.

4.6 Fertility, pregnancy and lactation

Pregnancy

ETORICOXIB AUSTELL is contraindicated in pregnancy (see sections 4.3 and 4.4). As with other medicines inhibiting prostaglandin synthesis, etoricoxib, as in ETORICOXIB AUSTELL, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester. If a woman becomes pregnant during treatment, ETORICOXIB AUSTELL must be discontinued.

The use of NSAIDS, such as ETORICOXIB AUSTELL used at 20 weeks gestation or later may cause serious kidney problems in an unborn baby.

After around 20 weeks of pregnancy, the unborn babies' kidneys produce most of the amniotic fluid. Amniotic fluid provides a protective cushion and helps the unborn babies' lungs, digestive system, and muscles develop. Foetal renal dysfunction can lead to oligohydramnios due to the low levels of amnionic fluid. Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation (see sections 4.2 and 4.4).

Lactation

ETORICOXIB AUSTELL is contraindicated in lactation (see section 4.3).

Mothers on ETORICOXIB AUSTELL should not breastfeed their infants.

Fertility

As with any medicine known to inhibit COX-2, the use of etoricoxib (such as in ETORICOXIB AUSTELL), 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 ETORICOXIB AUSTELL should refrain from driving or operating machinery.

4.8 Undesirable effects

a. Summary of the safety profile

It is reported that in clinical trials, etoricoxib was evaluated for safety in patients with OA, RA, chronic low back pain or ankylosing spondylitis (some patients with OA or RA were treated for one year or longer) and that the undesirable effects profile was similar in patients with OA or RA treated with etoricoxib for one year or longer.

In a clinical study for acute gouty arthritis, it is reported that patients were treated with etoricoxib 120 mg once daily for eight days and the adverse experience profile was generally similar to that reported in the combined OA, RA, and chronic low back pain studies.

In a cardiovascular safety outcomes programme of pooled data from three active comparator-controlled trials, it is reported that patients with OA or RA were treated with etoricoxib (60 mg or 90 mg) for a mean duration of approximately 18 months.

In clinical studies for acute postoperative dental pain following surgery, it is reported that patients treated with etoricoxib (90 mg or 120 mg), the adverse experience profile in these studies was generally similar to that reported in the combined OA, RA, and chronic low back pain studies.

b. Tabulated list of adverse reactions

The following undesirable effects were reported at an incidence greater than placebo in clinical trials in patients with OA, RA, chronic low back pain or ankylosing spondylitis treated with etoricoxib 30 mg, 60 mg or 90 mg up to the recommended dose for up to 12 weeks; in some long-term studies for up to 3½ years; in short-term acute pain studies for up to 7 days; or in post-marketing experience (see Table 1):

Table 1

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Infections and infestations	alveolar osteitis	gastroenteritis, upper respiratory infection, urinary tract infection	
Blood and lymphatic system disorders		anaemia (primarily associated with gastrointestinal bleeding), leukopenia, thrombocytopenia	
Immune system disorders		hypersensitivity*$^{\beta}$, angioedema/anaphylactic /anaphylactoid reactions including shock*	
Metabolism and nutrition disorders	oedema/fluid retention	appetite increase or decrease, weight gain	
Psychiatric disorders		anxiety,	

		depression, mental acuity decreased, hallucinations*, confusion*, restlessness*	
Nervous system disorders	dizziness, headache	dysgeusia, insomnia, paraesthesia/hypaesthesia, somnolence	
Eye disorders		blurred vision, conjunctivitis	
Ear and labyrinth disorders		tinnitus, vertigo	
Cardiac disorders	palpitations, dysrhythmia*	atrial fibrillation, tachycardia*, congestive heart failure, non-specific ECG changes,	

		angina, pectoris*, myocardial infarction[#]	
Vascular disorders	hypertension	flushing, cerebrovascular accident[#], transient ischaemic attack, hypertensive crisis*, vasculitis*	
Respiratory, thoracic and mediastinal disorders	bronchospasm*	cough, dyspnoea, epistaxis	
Gastrointestinal disorders	abdominal pain, constipation, flatulence, gastritis, heartburn/acid reflux, diarrhoea,	abdominal distention, bowel movement pattern change, dry mouth, gastroduodenal ulcer, peptic ulcers including gastrointestinal perforation and bleeding,	

	dyspepsia/epigastric discomfort, nausea, vomiting, oesophagitis, oral ulcer	irritable bowel syndrome, pancreatitis*	
Hepatobiliary disorders	ALT increased, AST increased	hepatitis*, hepatic failure*, jaundice*	
Skin and subcutaneous tissue disorders	ecchymosis	facial oedema, pruritus, rash, erythema*, urticaria*, Stevens-Johnson syndrome*, toxic epidermal necrolysis*, fixed drug eruption*	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)* (see section 4.4)

Musculoskeletal and connective tissue disorders		muscular cramp/spasm, musculoskeletal pain/stiffness	
Renal and urinary disorders		proteinuria, serum creatinine increased, renal failure/renal insufficiency* (see section 4.4)	
General disorders and administration site conditions	asthenia/fatigue, flu-like disease	chest pain	
Investigations		blood urea nitrogen increased, creatine phosphokinase increased, hyperkalaemia, uric acid increased, blood sodium decreased	

* This adverse reaction was identified through post-marketing surveillance.

β Hypersensitivity includes the terms “allergy”, “drug allergy”, “drug hypersensitivity”, “hypersensitivity”, “hypersensitivity NOS”, “hypersensitivity reaction” and “nonspecific allergy”.

[#] Based on analyses of long-term placebo and active controlled clinical trials, it is reported that selective COX-2 inhibitors have been associated with an increased risk of serious thrombotic arterial events, including myocardial infarction and stroke.

c. Description of selected adverse reactions

Serious undesirable effects have been reported in association with the use of NSAIDs and cannot be ruled out for ETORICOXIB AUSTELL: nephrotoxicity including interstitial nephritis and nephrotic syndrome; hepatotoxicity including hepatic failure and pancreatitis.

Reporting of suspected adverse reactions

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

4.9 Overdose

It is reported that in clinical studies, administration of single doses of etoricoxib up to 500 mg and multiple doses up to 150 mg/day for 21 days did not result in significant toxicity. There have been reports of acute overdosage with etoricoxib, although adverse experiences were not reported in the majority of cases.

Symptoms

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

Management

In the event of overdose, the usual supportive measures should be employed such as remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, as necessary.

Haemodialysis will not be of value in management of ETORICOXIB AUSTELL overdose. It is not known whether etoricoxib is removed by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A.3.1 Anti-Rheumatics (anti-inflammatory agents)

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, coxibs, ATC code: M01 AH05

Mechanism of Action

Etoricoxib is a nonsteroidal anti-inflammatory drug (NSAID) which selectively inhibits cyclo-oxygenase-2 (COX-2). In animal models, etoricoxib has been shown to exhibit anti-inflammatory, analgesic and antipyretic activities. Etoricoxib did not inhibit

gastric prostaglandin synthesis and had no effect on platelet function.

Cyclooxygenase is responsible for generation of prostaglandins. Cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2) are the two isoforms of the enzyme cyclo-oxygenase that have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.

5.2 Pharmacokinetic properties

Absorption

Etoricoxib is well absorbed following oral administration with a mean oral bioavailability of approximately 100 %.

Following 120 mg once-daily dosing to steady state, the peak plasma concentration (geometric mean C_{max} equal to 3,6 µg/mL) was observed at approximately 1 hour (T_{max}) after administration to fasted adults. The geometric mean $AUC_{0\text{-}24hr}$ was 37,8 µg/hr/mL. Etoricoxib shows linear pharmacokinetics across the clinical dosage range. Onset of action (in studies specifically designed to measure such) has been shown to occur as early as 24 minutes following dosage administration.

No clinically meaningful effect on the extent or the rate of absorption of a dose of etoricoxib 120 mg was observed when administered with a standard meal. Etoricoxib has been administered without regard to food.

Distribution

Plasma protein binding of etoricoxib is approximately 92 % over the range of concentrations of 0,05 µg/mL to 5 µg/mL. At steady state, volume of distribution (V_{dss}) is approximately 120 litres.

Etoricoxib crosses the placenta and the blood-brain barrier.

Biotransformation

Etoricoxib undergoes extensive metabolism in the liver with less than 1 % of dose recovered in urine as the parent compound. The major route of metabolism of etoricoxib is via cytochrome P450 (CYP) enzymes to form the 6'-hydroxymethyl derivative. This derivative is then oxidised to form the major metabolite of etoricoxib (the 6'-carboxylic acid derivative). CYP3A4 appears to contribute to the metabolism of etoricoxib *in vivo*. *In vitro* studies indicate that CYP2D6, CYP2C9, CYP1A2 and CYP2C19 also can catalyse the main metabolic pathway, but their quantitative roles *in vivo* have not been studied.

Five metabolites have been identified in man. 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

Elimination of etoricoxib occurs almost exclusively through metabolism followed by renal excretion (70 %) and some faecal excretion (20 %). Less than 2 % is recovered as unchanged etoricoxib.

Following once-daily administration of etoricoxib (120 mg), steady state concentrations are reached within seven days, 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 specific groups of subjects or patients

Elderly population

Pharmacokinetic properties in the elderly (65 years of age and older) with normal renal function are similar to those in the young. In clinical studies a higher incidence of adverse experiences was seen in older patients compared to younger patients (see section 4.2).

Gender

The pharmacokinetics of etoricoxib are similar between men and women.

Hepatic impairment

Higher mean AUC values (by approximately 16 %) were observed when patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) were administered etoricoxib 60 mg once daily 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 sections 4.2 and 4.3).

Renal impairment

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) (see section 4.3).

Paediatric population

The pharmacokinetics of etoricoxib in paediatric patients (less than 12 years of age) has not been studied. In pharmacokinetic studies conducted in adolescents weighing 40 kg to 60 kg given etoricoxib 60 mg once daily and adolescents greater than 60 kg given etoricoxib 90 mg once daily were similar to the pharmacokinetics in adults given etoricoxib 90 mg once daily. Safety and efficacy of etoricoxib in paediatric and adolescent patients have not been established (see section 4.3).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

calcium hydrogen phosphate anhydrous

croscarmellose sodium

hydroxypropyl cellulose

lactose monohydrate

magnesium stearate

microcrystalline cellulose.

Tablet coating

30 mg tablets contain Opadry II Green 32K510009 (consisting of hypromellose, lactose monohydrate, titanium dioxide, triacetin, FD & C blue #2 (indigo carmine aluminium lake), iron oxide yellow).

60 mg tablets contain Opadry II Green 32K510012 (consisting of hypromellose, lactose monohydrate, titanium dioxide, triacetin, FD & C blue #2 (indigo carmine aluminium lake), iron oxide yellow).

90 mg tablets contain Opadry II White 32K580000 (consisting of hypromellose, lactose monohydrate, titanium dioxide, triacetin).

120 mg tablets contain Opadry II Green 32K510013 (consisting of hypromellose, lactose monohydrate, titanium dioxide, triacetin, FD & C blue #2 (indigo carmine aluminium lake), iron oxide yellow).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store in the original packaging until required for use.

Store at or below 25 °C. Protect from light.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

ETORICOXIB 30, 60, 90 and 120 mg AUSTELL are packed in silver aluminium/aluminium blister strips, in pack sizes of 10 (1 x 10), 30 (3 x 10), 60 (6 x 10), 7 (1 x 7), 14 (2 x 7) or 28 (2 x 14) tablets.

Not all pack sizes are necessarily marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Camox Pharmaceuticals (Pty) Ltd

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JOHANNESBURG

2193

South Africa

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8. REGISTRATION NUMBERS

ETORICOXIB 30 mg AUSTELL: 49/3.1/0988

ETORICOXIB 60 mg AUSTELL: 49/3.1/0989

ETORICOXIB 90 mg AUSTELL: 49/3.1/0990

ETORICOXIB 120 mg AUSTELL: 49/3.1/0991

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 April 2020

10. DATE OF REVISION OF THE TEXT

06 December 2021.