PROFESSIONAL INFORMATION

EXTRIB RANGE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

EXTRIB 30 mg film coated tablets

EXTRIB 60 mg film coated tablets

EXTRIB 90 mg film coated tablets

EXTRIB 120 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EXTRIB 30 mg: Each film coated tablet contains 30 mg etoricoxib and sugar (lactose monohydrate, 2,52 mg).

EXTRIB 60 mg: Each film coated tablet contains 60 mg etoricoxib and sugar (lactose monohydrate, 5,04 mg).

EXTRIB 90 mg: Each film coated tablet contains 90 mg etoricoxib and sugar (lactose monohydrate, 7,56 mg).

EXTRIB 120 mg: Each film coated tablet contains 120 mg etoricoxib and sugar (lactose monohydrate,10,08 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

EXTRIB 30 mg: Blue-green, apple-shaped, biconvex film coated tablets engraved ‘30’ on one face and other face plain.

EXTRIB 60 mg: Dark-green, apple-shaped, biconvex film coated tablets engraved ‘60’ on one face and other face plain.

EXTRIB 90 mg: White, apple-shaped, biconvex film coated tablets engraved ‘90’ on one face and other face plain.

EXTRIB 120 mg: Pale-green, apple-shaped, biconvex film coated tablets engraved ‘120’ on one face and other face plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EXTRIB is indicated for:

- symptomatic relief of osteoarthritis and rheumatoid arthritis
- treatment of ankylosing spondylitis
- 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.

4.2 Posology and method of administration

EXTRIB 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, 60 mg once daily may provide adequate therapeutic benefit.

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

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

Short term relief of acute pain: The recommended dose is 90 mg or 120 mg once daily, limited to a maximum of 8 days treatment.

Acute gouty arthritis: The recommended dose is 120 mg once daily, limited to a maximum of 8 days treatment.

Primary dysmenorrhoea: The recommended dose is 120 mg once daily.

Post-operative dental pain: The recommended dose is 90 mg once daily.

Doses of EXTRIB higher than those recommended above 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
- RA should not exceed 90 mg daily
- ankylosing spondylitis should not exceed 90 mg daily
- acute gout should not exceed 120 mg daily
- acute pain and primary dysmenorrhoea should not exceed 120 mg daily
- post-operative acute dental surgery pain should not exceed 90 mg daily.

As the cardiovascular risks of EXTRIB 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 EXTRIB is necessary for the elderly although they may be more susceptible to renal, gastrointestinal and cardiovascular side effects. When using EXTRIB in the elderly and in patients with renal, hepatic or cardiac dysfunction, medically appropriate supervision should be

intensified (see section 4.4). If patients show deterioration during treatment, appropriate measures should be undertaken, including discontinuation of EXTRIB.

Hepatic Insufficiency:

In patients with mild hepatic insufficiency (Child-Pugh score 5 to 6), a dose of 60 mg once daily should not be exceeded.

In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), the dose should be reduced; a dose of 60 mg every other day should not be exceeded. Administration of 30 mg once daily can also be considered.

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

Renal Insufficiency:

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

Paediatric population

EXTRIB is not indicated for use in children and adolescents under the age of 16 years (see section 4.3).

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).

Method of administration

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

Missed dose

Doctors should advise patients who forget to take EXTRIB to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

- known hypersensitivity to etoricoxib or to any of the ingredients of EXTRIB (see section 6.1)
- active peptic or a history of peptic ulceration or recurrent gastrointestinal perforation or bleeding (PUBs)
- severe hepatic dysfunction (Child-Pugh score > 9 or serum albumin < 25 g/litre)
- renal creatinine clearance < 30 mL/min
- signs of bronchospasm, asthma, acute rhinitis, nasal polyps, angioedema, urticaria or allergic-type reactions after taking aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) including EXTRIB
- uncontrolled hypertension
- inflammatory bowel disease
- congestive heart failure (NYHA II – IV)
- ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease (see section 4.4)
- peri-operative analgesia in the setting of coronary artery bypass surgery (CABG)
- pregnancy and lactation (see section 4.6)
- children and adolescents under 16 years of age
- lithium therapy: concomitant administration with EXTRIB 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

EXTRIB may predispose to cardiovascular events, gastrointestinal events or cutaneous reactions which may be fatal.

Long-term administration of NSAIDs such as EXTRIB have 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 EXTRIB may cause a reduction in prostaglandin formation and secondarily in renal blood flow, and thereby impair renal function. Patients at greatest risk of this response are those with pre-existing significantly impaired renal function, uncompensated heart failure or liver cirrhosis. Monitoring of renal and hepatic function in such patients is indicated.

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

Fluid retention, oedema and hypertension have been observed in patients taking etoricoxib, as in EXTRIB, due to inhibition of prostaglandin synthesis. All nonsteroidal anti-inflammatory drugs (NSAIDs), including EXTRIB, 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 for any other reason. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of EXTRIB should be taken.

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

Clinical trials suggest that the selective COX-2 inhibitor class of medicines, such as EXTRIB, are associated with an increased risk of thrombotic events (especially myocardial infraction and stroke). As the cardiovascular risks of EXTRIB 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.

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

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

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

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

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

Gastrointestinal effects:

Upper gastrointestinal complications (perforations, ulcers or bleedings), some of them resulting in fatal outcome, have occurred in patients treated with EXTRIB. Therefore, EXTRIB should be used with caution in patients with a history of, or at risk of developing, such events.

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

There is an increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) when EXTRIB is taken concomitantly with the following medicines: aspirin (even at low doses), other NSAIDs, corticosteroids.

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 treated for up to 1 year with etoricoxib 60 mg and 90 mg daily, as in EXTRIB.

Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test (3 times the upper limit of normal) has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests are detected, EXTRIB should be discontinued.

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

The use of EXTRIB is not recommended in fertile women attempting to conceive (see section 4.6).

Information on excipients of EXTRIB:

EXTRIB contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take EXTRIB.

EXTRIB contains lactose monohydrate which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Ciclosporin and tacrolimus: The nephrotoxic effect of ciclosporin or tacrolimus may be increased if co-administered with any NSAID including EXTRIB. Renal function should be monitored when EXTRIB and either of these medicines is used in combination.

Warfarin: Warfarin therapy, when administered with EXTRIB is associated with an increase (13 %) in prothrombin time International Normalised Ratio (INR). Standard monitoring of INR values should be conducted when therapy with EXTRIB is initiated or changed in patients receiving warfarin or similar oral anticoagulants.

Rifampicin: Co-administration of EXTRIB with rifampicin, a potent inducer of hepatic metabolism, may significantly decrease the plasma AUC concentration of etoricoxib. This interaction should be considered when EXTRIB is co-administered with rifampicin.

Methotrexate: Monitoring for methotrexate-related toxicity should be considered when EXTRIB, at doses > 90 mg daily, and methotrexate are administered concomitantly, since EXTRIB may increase the plasma concentration and reduce the renal clearance of 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 %.

Diuretics, Angiotensin Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs): Reports suggest that non-selective NSAIDs and COX-2 selective inhibitors such as EXTRIB may reduce the antihypertensive effect of diuretics, ACE inhibitors and ARBs.
This interaction should be given consideration in patients taking EXTRIB together with these medicines. In patients with compromised renal function (e.g. elderly patients or patients who are volume depleted, including those on diuretic therapy) who are being treated with EXTRIB, the co-administration of ACE inhibitors or ARBs may result in a further deterioration of renal function, including possible acute renal failure. These effects may be reversible. Therefore, the combination should be administered with caution, especially in the elderly and in patients with impaired renal function. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Lithium: Reports suggest that EXTRIB may increase plasma lithium levels. This interaction should be given consideration in patients taking EXTRIB concomitantly with lithium.

Aspirin, NSAIDs and other medications which may increase the risk of gastrointestinal adverse events: EXTRIB may be used concomitantly with aspirin at doses used for cardiovascular prophylaxis (low-dose aspirin). However, concomitant administration of low-dose aspirin with EXTRIB increases the rate of gastrointestinal ulceration, and other complications compared to use of EXTRIB alone. Concomitant administration of EXTRIB with doses of aspirin above those for cardiovascular prophylaxis or with other NSAIDs should be avoided. Corticosteroids may also increase the risk of gastrointestinal side effects (see section 4.4).

Oral Contraceptives: EXTRIB 60 mg given concomitantly with an oral contraceptive containing 35 µg ethinylestradiol (EE) and 0,5 mg to 1 mg norethindrone (NET) for 21 days, increased the steady state AUC_{0-24h} of EE by 37 %. EXTRIB 120 mg given with the same oral contraceptive concomitantly or separated by 12 hours, increased the steady state AUC_{0-24h} of EE by 50 % to 60 %; however, (NET) concentrations generally did not increase to a clinically relevant degree.
This increase in EE concentration should be considered when selecting an appropriate oral contraceptive for use with EXTRIB. An increase in EE exposure can increase the incidence of adverse events associated with oral contraceptives (e.g. venous thromboembolic events in women at risk).

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

Hormone Replacement Therapy: Administration of EXTRIB 120 mg with hormone replacement therapy consisting of conjugated oestrogens (0,625 mg conjugated oestrogens for 8 days, increased the mean steady state AUC_{0-24h} of unconjugated oestrone (41 %), equilin (76 %) and 17-beta-oestradiol (22 %). The effect of the recommended chronic doses of EXTRIB (60 mg and 90 mg) has not been studied. The effects of EXTRIB 120 mg on the exposure (AUC_{0-24h}) to these oestrogenic components of conjugated oestrogens were less than half of those observed, when conjugated oestrogens were 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 EXTRIB. These increases in oestrogenic concentration should be taken into consideration when selecting post-menopausal hormone therapy for use with EXTRIB, because the increase in oestrogen exposure might increase the risk of adverse events associated with Hormone Replacement Therapy (HRT).

Effects of EXTRIB on medicines metabolised by sulfotransferases:

EXTRIB is an inhibitor of sulfotransferase activity, particularly SULT1E1, and has been shown to increase the serum concentrations of ethinylestradiol. While knowledge about the effects of multiple

sulfotransferases are presently limited, and the clinical consequences for many medicines are still being examined, it may be prudent to exercise care when administering EXTRIB concurrently with other medicines primarily metabolised by human sulfotransferases (e.g. oral salbutamol and minoxidil).

Other:

Etoricoxib, as in EXTRIB, does not display clinically significant effects on the pharmacokinetics of prednisone/prednisolone, nor alter the steady-state plasma $AUC_{0\text{-}24hr}$ or renal elimination of digoxin. An increase in digoxin C_{max} (approximately 33 %) has been observed (see section 4.3). Patients at high risk of digoxin toxicity should be monitored for this when EXTRIB and digoxin are administered concomitantly.

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

Ketoconazole, a potent inhibitor of CYP3A4, does not have any clinically important effect on the single-dose pharmacokinetics of EXTRIB.

Etoricoxib, as in EXTRIB, has been used concomitantly with a wide range of commonly prescribed medicines without evidence of clinical adverse interactions.

4.6 Fertility, pregnancy and lactation

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

Pregnancy

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

Breastfeeding

Mothers on EXTRIB should not breastfeed their infants.

Fertility

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

4.7 Effects on ability to drive and use machines

The effect of EXTRIB on the ability to drive or use machines has not been studied. Patients who experience dizziness, vertigo or somnolence while taking EXTRIB should refrain from driving or operating machinery.

4.8 Undesirable effects

Tabulated summary of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	*Frequent* *Less frequent*	Alveolar osteitis Gastroenteritis, upper respiratory infection, urinary tract infection
Blood and lymphatic system disorders	*Less frequent* *Frequency unknown*	Anaemia (primarily associated with gastrointestinal bleeding), leukopenia Thrombocytopenia
Immune system disorders	*Frequency unknown*	Hypersensitivity, angioedema, anaphylactic/anaphylactoid reactions including shock
Metabolism and nutrition disorders	*Frequent* *Less frequent*	Oedema/fluid retention Appetite increase or decrease, weight gain
Psychiatric disorders	*Less frequent* *Frequency unknown*	Anxiety, depression, mental acuity decreased Confusion, hallucinations, restlessness

Nervous system disorders	*Frequent* *Less frequent* *Frequency unknown*	Dizziness, headache Insomnia, paraesthesia/ hypaesthesia, dysgeusia Somnolence, cerebrovascular incidents (strokes)
Eye disorders	*Less frequent* *Frequency unknown*	Conjunctivitis Blurred vision
Ear and labyrinth disorders	*Less frequent*	Tinnitus, vertigo
Cardiac disorders	*Frequent* *Less frequent* *Frequency unknown*	Palpitations Atrial fibrillation, congestive heart failure, nonspecific ECG changes, myocardial infarction, angina pectoris, cardiovascular thrombotic events Dysrhythmia and tachycardia have been reported regardless of causality, congestive heart failure
Vascular disorders	*Frequent* *Less frequent* *Frequency unknown*	Hypertension, aggravated hypertension Flushing, transient ischaemic attack Hypertensive crisis, peripheral oedema
Respiratory, thoracic and mediastinal disorders	*Less frequent* *Frequency unknown*	Cough, dyspnoea, epistaxis Bronchospasm

Gastrointestinal disorders	*Frequent* *Less frequent* *Frequency unknown*	Gastrointestinal disorders (e.g. abdominal pain, flatulence, heartburn), diarrhoea, dyspepsia, epigastric discomfort, nausea Abdominal distension, acid reflux, bowel movement pattern change, dry mouth, gastro-duodenal ulcer, irritable bowel syndrome, peptic ulcer including GI perforation and bleeding, pancreatitis, constipation, gastritis, vomiting, oesophagitis, oral ulcer Melaena, haematemesis, ulcerative colitis, exacerbation of colitis and Crohn's disease
Hepatobiliary disorders	*Frequency unknown*	Hepatotoxicity including hepatic failure, hepatitis, jaundice
Skin and subcutaneous tissue disorders	*Frequent* *Frequency unknown*	Ecchymosis Facial oedema, pruritus, rash, erythema, urticaria, bulbous reactions including Stevens Johnson syndrome and toxic epidermal necrolysis, fixed drug eruption
Musculoskeletal, connective tissue and bone disorders	*Less frequent*	Muscular cramp/spasm, musculoskeletal pain/stiffness
Renal and urinary disorders	*Less frequent* *Frequency unknown*	Proteinuria Renal insufficiency including renal failure, nephrotoxicity including interstitial nephritis and nephrotic syndrome
General disorders and administrative site conditions	*Frequent* *Less frequent*	Asthenia/fatigue, flu-like disease Chest pain

Investigations	*Frequent* *Less frequent*	ALT increased, AST increased Blood urea increased, creatine phosphokinase increased, haematocrit decreased, haemoglobin decreased, hyperkalaemia, leukocytes decreased, platelets decreased, serum creatinine increased, uric acid increased, blood sodium decreased

The following serious undesirable effects have been reported in association with the use of NSAIDs and cannot be ruled out for EXTRIB: 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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms

The most frequently observed adverse experiences were gastrointestinal and renovascular events.

Management of overdose

In the event of overdose, the usual supportive measures can be employed e.g. remove unabsorbed material from the gastrointestinal tract and clinically monitor, and institute supportive therapy if required.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, coxibs

ATC code: M01AH05

Pharmacological classification: A.3.1 Anti-Rheumatics (Anti-inflammatory Agents)

Mechanism of action

Etoricoxib is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic activities in animal models. Etoricoxib is an orally active COX-2-selective inhibitor.

5.2 Pharmacokinetic properties

Absorption:

Etoricoxib has a mean oral bioavailability of approximately 100 %. Peak plasma concentrations (geometric mean C_{max} equal to 36 µg/mL) occur in about 1 hour (T_{max}) in fasted adults. The geometric mean $AUC_{0\text{-}24hr}$ is 37,8 µg/hr/mL. The extent or rate of absorption of a dose of etoricoxib 120 mg is not clinically meaningfully affected by a standard meal.

Food has no clinically meaningful effect on the extent or rate of etoricoxib absorption.

The pharmacokinetics of etoricoxib is shown to be similar (comparable AUC, C_{max} within approximately 20 %) when administered alone or with a magnesium/aluminium hydroxide antacid or a calcium carbonate antacid.

Distribution:

Etoricoxib is approximately 92 % bound to plasma protein over the range of concentrations of 0,05 µg/mL to 5 µg/mL. The volume of distribution at steady state (Vdss) is approximately 120 litres.

Etoricoxib crosses the placenta and the blood-brain barrier.

Biotransformation:

Etoricoxib is extensively metabolised in the liver with < 1 % of a dose recovered in urine as the parent-compound. The major route of metabolism is via cytochrome P450 isoenzymes, to form the 6'-hydroxymethyl derivative.

Five metabolites have been identified. The main metabolite is the 6'-carboxylic acid derivative of etoricoxib formed by further oxidation of the 6'-hydroxymethyl derivative. These principal metabolites either demonstrate no measurable activity or are only weakly active as COX-2 inhibitors.

Elimination:

Etoricoxib (single radiolabelled 25 mg intravenous dose) is extensively metabolised before excretion (approximately 70 % recovered in urine and 20 % in faeces), mostly as metabolites. Less than 2 % of a dose is recovered as unchanged.

Steady state concentrations of etoricoxib are reached within 7 days, with an accumulation ratio of 2, corresponding to an accumulation half-life of approximately 22 hours. The plasma clearance is estimated to be approximately 50 mL/min.

Linearity/non-linearity:

The pharmacokinetics of etoricoxib are linear across the clinical dose range.

Pharmacokinetics in special patient groups

Elderly:

Pharmacokinetics 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).

Hepatic insufficiency:

Patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) administered etoricoxib 60 mg once daily (for 21 days), had an approximately 16 % higher mean AUC as compared to healthy subjects given the

same regimen. Patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9) administered etoricoxib 60 mg every other day (for 21 days), had similar mean AUC to the healthy subjects given etoricoxib 60 mg once daily. There are no available clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score > 9) (see sections 4.3 and 4.2).

Renal insufficiency:

The pharmacokinetics of a single dose of etoricoxib 120 mg in patients with moderate (creatinine clearance 30 to 50 mL/min) to severe (creatinine clearance of < 30 mL/min) renal insufficiency, and patients with end-stage renal disease on haemodialysis, were not significantly different from those in healthy subjects. Haemodialysis contributed negligibly to elimination (dialysis clearance approximately 50 mL/min).

Paediatric population

The pharmacokinetics of etoricoxib in paediatric patients (< 12 years of age) has not been studied.
In a pharmacokinetic study (n=16) 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 > 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).

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores:

Calcium hydrogen phosphate anhydrous

Croscarmellose sodium

Hydroxypropyl cellulose

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose.

Film coating:

Opadry II Green (30 mg, 60 mg and 120 mg tablets)

HPMC 2910/Hypromellose 15 cP

Lactose Monohydrate

Titanium Dioxide

Triacetin

FD & C Blue # 2/Indigo Carmine aluminium lake (3% - 5%)

Iron oxide yellow.

Opadry II White (90 mg tablets only)

HPMC 2910/Hypromellose 15 cP

Lactose Monohydrate

Titanium Dioxide

Triacetin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store at or below 25° C.

Keep blisters in the carton until required for use.

6.5 Nature and contents of container

EXTRIB tablets are available in silver aluminium blister strips, packed inside an outer carton.

Each pack contains 7, 10, 28 or 30 tablets consisting or either 7 or 10, tablets per blister.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBER(S)

EXTRIB 30 mg: A50/3.1/0234

EXTRIB 60 mg: A50/3.1/0235

EXTRIB 90 mg: A50/3.1/0236

EXTRIB 120 mg: A50/3.1/0237

9. DATE OF FIRST AUTHORISATION

Date of registration: 15 June 2020

10. DATE OF REVISION OF THE TEXT

25 June 2024