SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE:

TOREFLAM 60

TOREFLAM 90

TOREFLAM 120

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each **TOREFLAM** 60 film coated tablet contains 60 mg of etoricoxib.

Contains Sugar: Lactose monohydrate 1,68 mg per tablet

Each **TOREFLAM** 90 film coated tablet contains 90 mg of etoricoxib.

Contains sugar: Lactose monohydrate 2,52 mg per tablet

Each **TOREFLAM** 120 film coated tablet contains 120 mg of etoricoxib.

Contains sugar: Lactose monohydrate 3,36 mg per tablet.

3. PHARMACEUTICAL FORM:

Film-coated tablets.

TOREFLAM 60: A green, round, biconvex, film-coated tablet debossed with ‘444’ on one side and ‘**L**’ on the other side.

TOREFLAM 90: A white to off-white, round, biconvex, film-coated tablet debossed with '445' on one side and '**L**' on the other side.

TOREFLAM 120: A pale-green, round, biconvex, film-coated tablet debossed with '446' on one side and '**L**' on the other side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

TOREFLAM is indicated for:

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

The decision to prescribe **TOREFLAM** 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

As the cardiovascular risks of TOREFLAM may increase with dose and duration of exposure, the lowest effective daily dose should be used, for the shortest possible duration of treatment.

Rheumatoid Arthritis (RA):

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

Special populations

Elderly

No dosage adjustment in **TOREFLAM** is necessary for the elderly although the elderly may be

more susceptible to renal, gastrointestinal and cardiovascular adverse effects (see section 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.

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 is use is contra-indicated in these patients (see **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 **TOREFLAM** in patients with creatinine clearance less than 30 ml/min is contraindicated (see section 4.3).

4.3 Contraindications

TOREFLAM is contraindicated in:

- Patients with known hypersensitivity to etoricoxib and or any of the excipients **TOREFLAM**
- Patients with active peptic ulceration or gastro-intestinal (GI) bleeding
- Patients with severe hepatic insufficiency (Child Pugh score greater than 9 or serum albumin less than 25 g/L)
- Patients with severe renal impairment (estimated creatinine clearance less than 30 ml/min)
- 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.

- Patients with hypertension whose blood pressure has not been adequately controlled
- Pregnancy and lactation (see section 4.4 and 4.6)
- Children and adolescents under 16 years of age
- Patients with inflammatory bowel disease
- Patients with congestive heart failure (NYHA II – IV)
- Heart failure, established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease (stroke)
- Perioperative analgesia in the setting of coronary artery bypass surgery (CABG)
- Lithium: Patients who are receiving concomitant lithium therapy as this may increase plasma levels of lithium (see **section 4.5**)
- Digoxin: Patients who are at high risk of digoxin toxicity as concomitant use. **TOREFLAM** with digoxin may increase C_{max} digoxin by approximately 33 %

4.4 Special warnings and precautions for use

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

Long-term administration of NSAIDs 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 **TOREFLAM** 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 **TOREFLAM** in patients with dehydration. It is advisable to rehydrate patients prior to starting therapy with **TOREFLAM.**

Fluid retention, oedema and hypertension have been observed in patients taking **TOREFLAM**. All Nonsteroidal Anti-inflammatory Drugs (NSAIDs), including etoricoxib, 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 **TOREFLAM** should be taken.

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

The selective COX-2 inhibitor class medicines may be associated with an increased risk of thrombotic events (especially MI and stroke), relative to placebo and some NSAIDs. As the cardiovascular risks of selective COX-2 inhibitors 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) should only be treated with **TOREFLAM** after careful consideration.

TOREFLAM is not a substitute for aspirin for cardiovascular prophylaxis because of its lack of effect on platelets. Because **TOREFLAM** 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 **TOREFLAM. (**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 NSAIDs and some selective COX-2 inhibitors during post-marketing surveillance (see section 4.8). These serious events may occur without warning. Patients appear to be at higher 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 **TOREFLAM** (see section 4.8). Some selective COX-2 inhibitors have been associated with an increased risk of skin reactions in patients with a history of allergy to medicines. **TOREFLAM** should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

When using **TOREFLAM** 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 **TOREFLAM.**

Caution is advised with treatment of patients most at risk of developing a gastro-intestinal complication with NSAIDs such as **TOREFLAM**; the elderly, patients using any other NSAID or acetylsalicylic acid concomitantly or patients with a prior history of gastro-intestinal disease such as 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 **TOREFLAM** is taken concomitantly with aspirin (acetylsalicylic acid) (even at low doses). 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 studies treated for up to one year with etoricoxib 60 mg and 90 mg daily. A patient with symptoms and/or signs suggesting liver impairment 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, **TOREFLAM** should be discontinued.

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

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

Due to inhibition of prostaglandin synthesis, fluid retention and oedema have been observed in patients taking **TOREFLAM**; therefore, **TOREFLAM** should be used with caution in patients with compromised cardiac function and other conditions predisposing to or worsened by fluid retention. Patients with pre-existing congestive heart failure or hypertension should be closely monitored. **TOREFLAM** should be used with caution or not at all in patients on warfarin**. TOREFLAM** inhibits platelet function and to some extent and has an irritant effect on the gastrointestinal tract, so increasing the risk of haemorrhage. **TOREFLAM** can increase the hypoprothrombinaemic effect of warfarin by an intrinsic effect on coagulation or by displacement of warfarin from plasma protein biding sites.

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as **TOREFLAM**. 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. Eosinophillia 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 **TOREFLAM** and evaluate the patient immediately.

TOREFLAM contains lactose

Patients with rare hereditary conditions such as galactose intolerance, the Lapp lactase deficiency or galactose mal-absorption should not take **TOREFLAM**.

4.5 Interaction with other medicines and other forms of interaction

Ciclosporin and tacrolimus:

Although this interaction has not been studied with **TOREFLAM**, co-administration of ciclosporin or tacrolimus with and NSAID may increase the nephrotoxic effect of ciclosporin or tacrolimus. Renal function should be monitored when **TOREFLAM** and either of these medicines is used in combination.

Warfarin:

In patients stabilised on chronic warfarin therapy, the administration of **TOREFLAM** 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 **TOREFLAM** is initiated or changed in patients receiving warfarin or similar medicines.

Rifampicin:

Co-administration of **TOREFLAM** 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 **TOREFLAM** is co-administered with rifampicin.

Methotrexate:

Two studies investigated the effects of **TOREFLAM** 60, 90 or 120 mg administered once daily for seven days in patients receiving once-weekly methotrexate doses of 7.5 to 20 mg for rheumatoid arthritis. **TOREFLAM** at 60 and 90 mg had no effect on methotrexate plasma concentrations or renal clearance. In one study, **TOREFLAM** 120 mg had no effect, but in the other study, **TOREFLAM** 120 mg increased methotrexate plasma concentrations by 28%

and reduced renal clearance of methotrexate by 13%. Methotrexate-related toxicity should be monitored when **TOREFLAM** at doses greater than 90 mg 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 **TOREFLAM** may diminish the antihypertensive effect of diuretics, ACE inhibitors and ARBs. This interaction should be given consideration in patients taking **TOREFLAM** 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 drugs, including selective COX-2 inhibitors, the co-administration of ACE inhibitors of AIIAs may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution, especially in the elderly and in patients with impaired renal function. Patients should be adequately rehydrated 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 **TOREFLAM** may increase plasma lithium levels. Should lithium blood levels in patients taking **TOREFLAM** concomitantly with lithium increase, **TOREFLAM** should be withdrawn.

Aspirin:

TOREFLAM can be used concomitantly with aspirin at doses used for cardiovascular prophylaxis (low dose aspirin). However, concomitant administration of low-dose aspirin with **TOREFLAM** increases the rate of GI ulceration or other complications compared to use of **TOREFLAM** alone. Concomitant administration of **TOREFLAM** with doses of aspirin above those for cardiovascular prophylaxis or with other NSAIDs should be avoided (see **section 4.8**).

Oral contraceptives:

TOREFLAM 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 $AUC_{0\text{-}24hr}$ of EE by 37 %. **TOREFLAM** 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 %. This increase in EE concentration should be considered when selecting an oral contraceptive for use with **TOREFLAM**. 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:

NSAIDs such as **TOREFLAM** reduce the natriuretic effect of furosemide and thiazides in patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Hormone Replacement Therapy:

Administration of **TOREFLAM** 120 mg with hormone replacement therapy consisting of conjugated oestrogens 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 **TOREFLAM (**60 mg and 90 mg) has not been studied. The effects of **TOREFLAM** 120 mg on the exposure ($AUC_{0\text{-}24hr}$) to these estrogenic components of conjugated oestrogen were less than half of those observed when conjugated oestrogen was administered alone and the dose was increased from 0,625 mg to 1,25 mg). The clinical significance of these increases is unknown, and higher doses of conjugated oestrogen were not studied in combination with **TOREFLAM**. These increases in oestrogenic concentration should be taken into consideration when selecting post-menopausal hormone therapy for use with **TOREFLAM** because the increase in oestrogen exposure might increase the risk of adverse events associated with hormone replacement therapy (HRT).

Effects of TOREFLAM on medicines metabolised by sulfotransferases:

TOREFLAM is an inhibitor of human sulfotransferases 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 **TOREFLAM** concurrently with other medicines primaril*y* metabolised by human sulfotransferases (e.g. oral salbutamol and minoxidil).

Digoxin:

TOREFLAM 120 mg once daily for 10 days in healthy volunteers did not alter the steady-state plasma AUC_0 – 24h or renal elimination of digoxin. There was an increase in digoxin C_{max}

(approximately 33 %) (see section 4.3)

Other:

in interaction studies, **TOREFLAM** did not have clinically important effects on the pharmacokinetics of prednisone/prednisolone.

TOREFLAM 120 mg once daily for 10 days in healthy volunteers did not alter steady state plasma $AUC_{0\text{-}24hr}$ or renal elimination of digoxin. There was an increase in digoxin C_{max} (approximately 33 %).

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

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 **TOREFLAM** (43 % increase in AUC).

4.6 Fertility, pregnancy, and lactation

Pregnancy:

Safety in pregnancy and lactation has not been established, **TOREFLAM** is contraindicated in pregnancy (see section 4.3)

The use of non-steroidal anti-inflammatory drugs such as **TOREFLAM** during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus in utero, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed and its duration increased.

Regular use of non-steroidal inflammatory drugs may result in:

First trimester

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies raise concern about an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1 %, up to approximately 1,5 %. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period

Second and Third trimester.

During the third trimester of pregnancy, prostaglandin synthesis inhibitors, may expose the foetus to: cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension); renal dysfunction, which may progress to renal failure with oligo-hydroamniosis.

At the end of pregnancy, the mother and the neonate may be exposed to: possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses; inhibition of uterine contractions resulting in delayed or prolonged labour.

Breastfeeding

TOREFLAM is contraindicated in lactation (see **4.3**). **TOREFLAM** is excreted in milk of lactating rats. Women taking **TOREFLAM** should not breastfeed their infants.

Fertility:

The effects of **TOREFLAM** in fertility are not known. The use of **TOREFLAM** is not recommended in women attempting to conceive.

Women of Childbearing Potential:

TOREFLAM can increase the incidence of adverse events associated with oral contraceptives (e.g. venous thrombo embolic events in women at risk).

4.7 Effects on the ability to drive and use machines

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

4.8 Undesirable effects

Infections and infestations

Frequent: post-dental extraction alveolar osteitis (dry socket)

Less frequent: gastro-enteritis, upper respiratory infection, urinary tract infection

Blood and lymphatic system disorders

Less frequent: anaemia, leucopenia

Frequency unknown: thrombocytopaenia

Immune system disorder

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

Metabolism and nutrition disorders

Frequent: oedema/fluid retention

Less Frequent: appetite increase or decrease, weight gain

Psychiatric disorders

Less Frequent: anxiety, depression, mental acuity decreased.

Frequency unknown: confusion, hallucinations and restlessness.

Nervous system disorder

Frequent: dizziness, headache,

Less Frequent: insomnia, paraesthesia/hypaesthesia,

Frequency unknown: dysgeusia, somnolence

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

Frequency unknown: dysrhythmia, tachycardia and cardiovascular thrombotic events

Vascular disorders

Frequent: hypertension.

Less Frequent: flushing, cerebrovascular accident, transient ischaemic attack, vasculitis

Frequency unknown: aggravated hypertension, hypertensive crisis, peripheral oedema.

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 distention, acid reflux, bowel movement pattern change, constipation, dry mouth, gastroduodenal ulcer,—irritable bowel syndrome, vomiting, oesophagitis, oral ulcer and pancreatitis

Frequency unknown: peptic ulcers including gastro-intestinal perforation and bleeding (mainly in the elderly)

Hepatobiliary disorders

Frequent: increased ALT, increased AST.

Less Frequent: hepatitis, jaundice, hepatic failure

Skin and subcutaneous tissue disorders

Frequent: ecchymosis

Less Frequent: facial oedema, pruritus, rash, erythema

Frequency unknown: urticarial, Stevens-Johnson syndrome, toxic epidermal necrolysis, fixed drug eruption, drug rash with eosinophilia and systemic symptoms (DRESS) (see section 4.4)

Musculoskeletal, connective tissue and bone disorders

Less Frequent: muscle cramp/spasms, musculoskeletal pain/stiffness

Renal and urinary disorders

Less Frequent: proteinuria, increased serum creatinine, renal insufficiency, including renal failure, may be reversible upon discontinuation of treatment (see section 5.2), nephrotoxicity including interstitial nephritis and nephrotic syndrome associated with NSAID's such as **TOREFLAM.**

General disorders and administration site conditions

Frequent: asthenia/fatigue, flu-like disease

Less Frequent: chest pain

Investigations

Less Frequent: 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 of **TOREFLAM**: Nephrotoxicity including interstitial nephritis and nephrotic syndrome; hepatoxicity.

Reporting side effects

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

4.9 Overdose

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

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.

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

5. Pharmacological properties

Category A, class 3.1 Antirheumatics (anti-inflammatory agents)

Pharmacotherapeutic group: Non-steroidal anti-inflammatory and antirheumatic drugs, NSAIDs, Coxibs, ATC code: M01AH01.

5.1 Pharmacodynamic properties

Etoricoxib is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic activities in animal models. Etoricoxib is an orally active, selective cyclo-oxygenase-2 (COX-2) inhibitor. COX-2 has been shown to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation and fever.

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 C_{max} equal to 3,6 mcg/mL]) was observed at approximately 1 hour (T_{max}) after administration to fasted adults. The geometric mean $AUC_{0\text{-}24hr}$ was 37,8 mcg/hr/mL]. The pharmacokinetics of etoricoxib is linear across the clinical dose range.

Food had no clinically meaningful effect on the extent or rate of absorption of a dose of etoricoxib 120 mg. During clinical trials, etoricoxib was administered without food.

The pharmacokinetics of etoricoxib were similar (comparable AUC, C_{max} 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 (V_{dss}) is approximately 120 L in humans.

Etoricoxib crosses the placenta and the blood-brain barrier.

Metabolism

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 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. 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.

Special Populations

Hepatic Impairment

Patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) administered etoricoxib 60 mg once daily 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 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).

Elderly patients

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. In clinical studies higher incidences of adverse experiences was seen in older patients compared to younger patients (see section 4.2)

Paediatric Population

The pharmacokinetics of etoricoxib in paediatric patients (less than 12 years of age) has not been studied. In the pharmacokinetic study 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 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

Calcium phosphate, croscarmellose sodium, hydroxy propyl cellulose, magnesium stearate, microcrystalline cellulose and opadry (hypromellose, lactose monohydrate, titanium dioxide, triacetin, Fd&C Blue number 2/indigo carmine aluminium lake, iron oxide yellow).

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C. Store in the original package in an outer carton. Protect from moisture.

Keep out of reach of children.

6.5 Nature and contents of container

TOREFLAM 60 mg tablets are available in aluminium foil and CFB foil or aluminium foil and PVC/PVDC foil or aluminium foil and PVC/PE/PVDC foil blister packs of 8's and 30's in an outer carton.

TOREFLAM 90 mg and 120 mg tablets are available in aluminium foil and CFB foil or aluminium foil and PVC/PVDC foil or aluminium foil and PVC/PE/PVDC foil blister packs of 8's and 30's in an outer carton.

6.6 Special precautions for disposal and other handling

No special requirements

7.Holder of certificate of registration

Innovata Pharmaceuticals (Pty) Ltd

Crownwood Office Park

100 Northern Parkway

Building D

Ormonde

Johannesburg

2091

8. Registration numbers

TOREFLAM 60: 50/3.1/0056.050

TOREFLAM 90: 50/3.1/0057.051

TOREFLAM 120: 50/3.1/0058.052

9. Date of first authorization/Renewal of the authorization

10 November 2020

10. Date of revision of the text

11 December 2021

REFERENCES:

Ref 1: Arcoxia

NAME AND ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

MSD (Pty) Ltd

117 16th Road

HALFWAY HOUSE

1685

DATE OF PUBLICATION OF THIS PACKAGE INSERT

Date on the registration certificate: 11 October 2013

Date of the most recently revised Professional Information: 31 March 2020

Ref 2:

Letter_to_Innovata_NSAIDs_Risk_of_Foetal_renal_impairment_PVC103_25Nov2020.docx

(1)

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs): RISK OF FOETAL RENAL DYSFUNCTION LEADING TO OLIGOHYDRAMNIOS AND, IN SOME CASES, NEONATAL RENAL IMPAIRMENT

Ref 3:

Letter_to_lnnovata_Pharmaceuticals_NSAIDs_Risk_of_DRESS_PVC109_Jul2021.

RE: NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) - RISK OF DRUG REACTION WITH EOSINOPHILLIA AND SYSTEMIC SYMPTOMS (DRESS)