SCHEDULING STATUS S3

1 NAME OF THE MEDICINE
CYRETIB 100, hard capsules
CYRETIB 200, hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each **CYRETIB 100** capsule contains 100 mg celecoxib.
Each **CYRETIB 200** capsule contains 200 mg celecoxib.

Contains sugar:

CYRETIB 100 contains 23,525 mg lactose monohydrate.
CYRETIB 200 contains 47,050 mg lactose monohydrate.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Hard capsules.
CYRETIB 100 mg capsules are opaque, white with blue bands on cap and body reverse printed white on blue bands with markings 100 on the body.
CYRETIB 200 mg capsules are opaque, white with gold bands on cap and body reverse printed white on gold bands with markings 200 on the body.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
- Symptomatic treatment of inflammation and pain in osteoarthritis and rheumatoid arthritis.
- Treatment of pain post dental surgery.
- Treatment of mild to moderate post-operative pain.
- Treatment of mild to moderate musculoskeletal pain.
- Treatment of mild to moderate primary dysmenorrhoea.
- Relief of symptoms of ankylosing spondylitis.

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

Osteoarthritis
The recommended daily dose is 200 mg, taken as a single dose or as two divided doses. Doses up to 400 mg per day have been studied.

Rheumatoid arthritis
The recommended daily dose is 100 mg or 200 mg twice per day.

Pain post-dental surgery
The recommended dose is 100 mg to 200 mg, up to a maximum daily dose of 400 mg. Dosing intervals should not be less than 4 hours.

Mild to moderate post-operative pain
The recommended dose is 200 mg once daily. Some patients may benefit from an additional 200 mg dose.

Mild to moderate musculoskeletal pain
The recommended dose is 200 mg twice daily.

Mild to moderate primary dysmenorrhea
The recommended dose is 400 mg initially, followed by an additional 200 mg dose if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily.

Ankylosing spondylitis
The recommended daily dose is 200 mg, taken as a single dose or as 100 mg twice daily. Some patients may benefit from a total daily dose of 400 mg.

Special populations
Hepatic impairment
No dosage adjustment is necessary in patients with mild hepatic impairment. Introduce **CYRETIB** at the lowest recommended dose in patients with moderate hepatic impairment. There is no clinical experience in patients with severe hepatic impairment. (See sections 4.3 and 5.2).

Renal impairment
No dosage adjustment is necessary in patients with mild or moderate renal impairment. There is no clinical experience in patients with severe renal impairment. (See sections 4.3 and 5.2).

Elderly
No dosage adjustment is necessary. However, for elderly patients with a body mass of 50 kg or less it is advisable to initiate therapy at the lowest recommended dose.

Children
As no data are available, **CYRETIB** is not recommended in persons under 18 years old.

Method of administration
Oral use. **CYRETIB** should be taken whole with a glass of water, with or without food.

4.3 Contraindications
- Hypersensitivity to celecoxib, or any other excipient of **CYRETIB** (see section 6.1).
- Known hypersensitivity to sulphonamide.
- Severe hepatic impairment (serum albumin < 25 g/L or Child-Pugh score > 10).
- Severe renal impairment with estimated creatinine clearance < 30 mL/min.
- Asthma, urticaria, or allergic-type reactions precipitated by aspirin or non-steroidal anti-inflammatory drugs (NSAIDs), including other cyclooxygenase-2 (COX-2) specific inhibitors.
- Established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease.
- Peri-operative analgesia against the background of coronary artery bypass surgery (CABG).
- Active peptic ulceration or gastrointestinal (GI) bleeding.
- Inflammatory bowel disease.
- In pregnancy and in women of childbearing potential unless using an effective method of contraception (see section 4.6). The potential for human risk in pregnancy is unknown but cannot be excluded.
- Breastfeeding (see section 4.6).

4.4 Special warnings and precautions

CYRETIB may predispose to cardiovascular incidents, cerebrovascular incidents, gastrointestinal events or cutaneous reactions that may be fatal.

Safety and efficacy of **CYRETIB** have not been established for treatment exceeding 12 weeks in osteoarthritis and 24 weeks in rheumatoid arthritis.

Cardiovascular effects
Increased number of serious cardiovascular (CV) events, mainly myocardial infarction, has been reported in patients with sporadic adenomatous polyps treated with celecoxib (as in **CYRETIB**) at doses of 200 mg twice daily and 400 mg twice daily, compared to placebo (see section 5.1).
As the cardiovascular risks of **CYRETIB** may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. NSAIDs, including COX-2 selective inhibitors, have been associated with increased risk of cardiovascular and thrombotic adverse events when taken long term. The exact magnitude of the risk associated with a single dose has not been determined, nor has the exact duration of therapy associated with increased risk. 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, 4.8 and 5.1).
Caution is advised when **CYRETIB** is prescribed to patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

CYRETIB is not a substitute for aspirin for prophylaxis of cardiovascular thromboembolic diseases because of their lack of antiplatelet effects. Therefore, antiplatelet therapies should not be discontinued.

Anaphylactoid reactions
As with NSAIDs in general, anaphylactoid reactions occurred in patients exposed to **CYRETIB** (see sections 4.3).

Gastrointestinal (GI) effects
Upper and lower gastrointestinal complications (perforations, ulcers or bleedings (PUBs)), some resulting in fatalities, have occurred in patients treated with celecoxib (as in **CYRETIB**). Caution is advised with treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or antiplatelet medicines (such as aspirin) or glucocorticoids concomitantly, patients using alcohol, or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.

When **CYRETIB** is taken concomitantly with aspirin (even at low doses), there is further increase in the risk of gastrointestinal adverse effects for celecoxib (gastrointestinal ulceration or other gastrointestinal complications).

A significant difference in GI safety between selective COX-2 inhibitors plus aspirin vs NSAIDs plus aspirin has not been demonstrated in long-term clinical trials.

Concomitant NSAID use
The concomitant use of **CYRETIB** and a non-aspirin NSAID should be avoided.

Fluid retention and oedema
Fluid retention and oedema have been observed in patients taking celecoxib (as in **CYRETIB**). Therefore, **CYRETIB** should be used with caution in patients with history of cardiac failure, left ventricular dysfunction or hypertension, and in patients with pre-existing oedema from any other reason, since prostaglandin inhibition may result in deterioration of renal function and fluid retention.

Caution is also required in patients taking diuretic treatment or otherwise at risk of hypovolaemia.

Patients with pre-existing congestive heart failure or hypertension should be closely monitored.

Hypertension
NSAIDs, including celecoxib (as in **CYRETIB**) can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. Therefore, blood pressure should be monitored closely during the initiation of therapy with **CYRETIB** and throughout the course of therapy.

Hepatic and renal effects
Compromised renal or hepatic function and especially cardiac dysfunction are more likely in the elderly and therefore medically appropriate supervision should be maintained.

NSAIDs, including **CYRETIB**, may cause renal toxicity. Celecoxib has shown renal effects similar to those observed with comparator NSAIDs. Patients at greatest risk for renal toxicity are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, angiotensin converting enzyme (ACE)-inhibitors, angiotensin II receptor antagonists, and the elderly (see section 4.5). Such patients should be carefully monitored while receiving treatment with **CYRETIB**.

Some cases of severe hepatic reactions, including fulminant hepatitis (some with fatal outcome), liver necrosis and hepatic failure (some with fatal outcome or requiring liver transplant), have been reported with celecoxib (contained in **CYRETIB**. Among the cases that reported time to onset, most of the severe adverse hepatic events developed within one month after initiation of celecoxib (contained in **CYRETIB** treatment (see section 4.8).
If during treatment, patients deteriorate in any of the organ system functions described above, appropriate measures should be taken and discontinuation of **CYRETIB** therapy should be considered.

Caution should be used when initiating treatment in patients with dehydration. It is advisable to first rehydrate patients and then commence with **CYRETIB** therapy.

CYP2D6 inhibition
Celecoxib inhibits CYP2D6. Although it is not a strong inhibitor of this enzyme, a dose reduction of **CYRETIB** may be necessary for individually dose-titrated medicines that are metabolised by CYP2D6 (see section 4.5).

CYP2C9 poor metabolisers
Patients known to be CYP2C9 poor metabolisers should be treated with caution.

Skin and systemic hypersensitivity reactions
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of celecoxib (as in **CYRETIB**), see section 4.8.
Patients appear to be at highest risk for these events early in the course of therapy: the onset of the event occurring in the majority of cases within the first month of treatment. Serious hypersensitivity reactions (including anaphylaxis, angioedema and drug rash with eosinophilia and systemic symptoms (DRESS), or hypersensitivity syndrome), have been reported in patients receiving celecoxib (as in **CYRETIB**), see section 4.8.
Patients with a history of sulphonamide allergy or any medicine allergy may be at greater risk of serious skin reactions or hypersensitivity reactions (see section 4.3). **CYRETIB** should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

General
CYRETIB may mask fever and other signs of inflammation.

Use with oral anticoagulants
In patients on concurrent therapy with warfarin, serious bleeding events, of which some were fatal, have been reported (see sections 4.8 and 4.5). Because increases in prothrombin time (INR) have been reported, anticoagulant activity should be closely monitored in patients receiving warfarin/coumarin-type oral anticoagulants, particularly when therapy with **CYRETIB** is initiated, or its dose is changed (see section 4.5). Concomitant use of anticoagulants with NSAIDS may increase the risk of bleeding. Caution should be exercised when combining **CYRETIB** with warfarin or other oral anticoagulants, including novel anticoagulants (e.g. apixaban, dabigatran, and rivaroxaban).

Excipients
CYRETIB 100 mg and 200 mg capsules contain lactose monohydrate (see sections 2 and 6.1). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose/galactose malabsorption should not take **CYRETIB**.

4.5 Interactions with other medicines and other forms of interaction
Pharmacodynamic interactions
Anticoagulants
In patients on concurrent therapy with warfarin, increases in prothrombin time (INR) have been reported (see section 4.4).
Anticoagulant activity should be monitored particularly in the first few days after initiating or changing the dose of **CYRETIB** in patients receiving warfarin or other anticoagulants since these patients have an increased risk of bleeding complications. Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with **CYRETIB** is initiated or its dose is changed (see section 4.4). Bleeding events in association with increases in prothrombin time (INR) have been reported, predominantly in the elderly, in patients receiving celecoxib (as in **CYRETIB**) concurrently with warfarin, some of them fatal.

Anti-hypertensives
NSAIDs, including **CYRETIB**, may reduce the effect of antihypertensive medicines (including ACE inhibitors, angiotensin II receptor antagonists, diuretics and beta-blockers). This interaction should be given consideration in patients taking **CYRETIB** concomitantly with antihypertensive medicines.

As for NSAIDs, the risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients, patients on diuretics or elderly patients) when ACE inhibitors or angiotensin II receptor antagonists, and/or diuretics are combined with NSAIDs, including **CYRETIB** (see section 4.4). Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Ciclosporin and tacrolimus
Co-administration of NSAIDs (including **CYRETIB**) and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin or tacrolimus, respectively. Renal function should be monitored when **CYRETIB** and any of these medicines are combined.

Aspirin
CYRETIB can be used with low-dose aspirin. However, concomitant administration of aspirin with **CYRETIB** may result in an increased rate of GI ulceration or other complications, compared to use of **CYRETIB** alone. Because of its lack of platelet effects, **CYRETIB** is not a substitute for aspirin for cardiovascular prophylaxis.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with **CYRETIB**.

An increased risk of gastrointestinal ulceration or other gastrointestinal complications compared to use of **CYRETIB** alone was shown for concomitant administration of low-dose aspirin.

Pharmacokinetic interactions
*Effects of **CYRETIB** on other medicines*
CYP2D6 inhibition
Celecoxib is an inhibitor of CYP2D6. The plasma concentrations of medicines that are substrates of this enzyme may be increased when **CYRETIB** is used concomitantly. Examples of medicines which are metabolised by CYP2D6 are antidepressants (tricyclics and SSRIs), neuroleptics, antidysrhythmic medicines, etc. The dose of individually dose-titrated CYP2D6 substrates may need to be reduced when treatment with **CYRETIB** is initiated or increased if treatment with **CYRETIB** is terminated.

Concomitant administration of celecoxib 200 mg twice daily resulted in 2,6-fold and 1,5-fold increases in plasma concentrations of dextromethorphan and metoprolol (CYP2D6 substrates), respectively. These increases are due to celecoxib CYP2D6 inhibition of the CYP2D6 substrate metabolism.

CYP2C19 inhibition
In vitro studies have shown some potential for celecoxib to inhibit CYP2C19 catalysed metabolism. The clinical significance of this in vitro finding is unknown. Examples of medicines which are metabolised by CYP2C19 are diazepam, citalopram and imipramine.

Methotrexate
In patients with rheumatoid arthritis celecoxib had no statistically significant effect on the pharmacokinetics (plasma or renal clearance) of methotrexate (in rheumatologic doses). However, adequate monitoring for methotrexate-related toxicity should be considered when combining these two medicines.

Lithium
In healthy persons, co-administration of celecoxib 200 mg twice daily with 450 mg twice daily of lithium resulted in a mean increase in Cmax of 16 % and in area under the curve (AUC) of 18 % of lithium. Therefore, patients on lithium treatment should be closely monitored when **CYRETIB** is introduced or withdrawn.

Oral contraceptives
In an interaction study, celecoxib had no clinically relevant effects on the pharmacokinetics of oral contraceptives (1 mg norethisterone/ 35 micrograms ethinylestradiol).

Glibenclamide/tolbutamide
Celecoxib does not affect the pharmacokinetics of tolbutamide (CYP2C9 substrate), or glibenclamide to a clinically relevant extent.

Phenytoin
In specific studies in healthy volunteers with other medicines metabolised by CYP2C9, celecoxib was found to produce no clinically significant pharmacokinetic interaction with phenytoin.

*Effects of other medicines on **CYRETIB***
CYP2C9 poor metabolisers
In individuals who are CYP2C9 poor metabolisers and demonstrate increased systemic exposure to celecoxib, concomitant treatment with CYP2C9 inhibitors such as fluconazole could result in further increases in celecoxib exposure. Such combinations should be avoided in known CYP2C9 poor metabolisers (see section 4.4).

CYP2C9 inhibitors and inducers
Since celecoxib is predominantly metabolised by CYP2C9, **CYRETIB** should be used at half the recommended dose in patients receiving fluconazole. Concomitant use of 200 mg single dose of celecoxib and 200 mg once daily of fluconazole, a potent CYP2C9 inhibitor, resulted in a mean increase in celecoxib Cmax of 60 % and in AUC of 130 %. Concomitant use of inducers of CYP2C9 such as rifampicin, carbamazepine and barbiturates may reduce plasma concentrations of celecoxib.

Ketoconazole and antacids
Ketoconazole or antacids have not been observed to affect the pharmacokinetics of celecoxib.

Paediatric populations
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation
Pregnancy
CYRETIB is contraindicated in pregnancy (see section 4.3)
CYRETIB may cause uterine inertia and premature closure of the ductus arteriosus and should be avoided during pregnancy.

Breastfeeding
Limited data indicate that **CYRETIB** is excreted in breast milk and must therefore not be used during lactation.

Fertility
Based on the mechanism of action, the use of NSAIDs, including **CYRETIB**, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women.

4.7 Effects on ability to drive and use machines
The effect of celecoxib on ability to drive or use machinery has not been studied but based on its pharmacodynamic properties and overall safety profile it is unlikely to have an effect. Patients who experience dizziness, vertigo or somnolence (see section 4.8) while taking **CYRETIB** should refrain from driving or operating machinery.

4.8 Undesirable effects
Tabulated list of adverse reactions

Infections and infestations	
Frequent:	Sinusitis, upper respiratory tract infection, pharyngitis, urinary tract infection, bronchitis
Less frequent:	Helicobacter infection, herpes zoster, erysipelas, bronchopneumonia, labyrinthitis, gingival infection
Blood and the lymphatic system disorders	
Less frequent:	Anaemia, leukopenia, thrombocytopenia, pancytopenia, agranulocytosis, ecchymosis
Immune system disorders	
Frequent:	Hypersensitivity, allergy aggravated
Less frequent:	Anaphylactic shock, anaphylactic reaction, angioedema
Frequency unknown:	Anaphylaxis
Metabolism and nutrition disorders	
Frequent:	Increased weight
Less frequent:	Hyperkalaemia, increased blood sodium
Psychiatric disorders	
Frequent:	Insomnia
Less frequent:	Anxiety, depression, fatigue, confusional state, hallucinations
Nervous system disorders	
Frequent:	Dizziness, hypertonia, headache
Frequency unknown:	Cerebral infarction (stroke), paraesthesia, somnolence, ataxia, dysgeusia, intracranial haemorrhage (including fatal intracranial haemorrhage), aseptic meningitis, epilepsy (including aggravated epilepsy), ageusia, anosmia
Eye disorders	
Less frequent:	Blurred vision, conjunctivitis, eye haemorrhage, retinal artery occlusion, retinal vein occlusion, vitreous floaters, conjunctival haemorrhage
Ear and labyrinth disorders	
Less frequent:	Tinnitus, hypoacusis, dysphonia
Cardiac disorders	
Frequent:	Myocardial infarction, angina pectoris
Less frequent:	Cardiac failure, palpitations, tachycardia, dysrhythmia
Frequency unknown:	Cardiovascular thrombotic incidents
Vascular disorders	
Frequent:	Hypertension (including aggravated hypertension)
Less frequent:	Pulmonary embolism, flushing, vasculitis, deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	
Frequent:	Rhinitis, cough, dyspnoea
Less frequent:	Bronchospasm, pneumonitis
Gastrointestinal disorders	
Frequent:	Nausea, abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting, dysphagia, irritable bowel syndrome, tooth disorder
Less frequent:	Constipation, gastritis, stomatitis, gastrointestinal inflammation (including aggravation of gastrointestinal inflammation), eructation, gastrointestinal haemorrhage, duodenal ulcer, gastric ulcer, oesophageal ulcer, intestinal ulcer, large intestinal ulcer, intestinal perforation, oesophagitis, melaena, pancreatitis, colitis, haemorrhoidal haemorrhage, frequent bowel movements, mouth ulceration
Hepatobiliary disorders	
Less frequent:	Abnormal hepatic function, increased hepatic enzymes (including increased AST and ALT), hepatitis, hepatic failure (sometimes fatal or requiring liver transplant), fulminant hepatitis (some with fatal outcome), hepatic necrosis, cholestasis, cholestatic jaundice
Skin and subcutaneous tissue disorders	
Frequent:	Rash, pruritus (includes generalised pruritus)
Less frequent:	Urticaria, ecchymosis, alopecia, photosensitivity, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), bullous dermatitis, lipoma, allergic dermatitis, ganglion
Musculoskeletal and connective tissue disorders	
Frequent:	Arthralgia
Less frequent:	Muscle spasms (leg cramps), myositis, lower limb fracture
Renal and urinary disorders	
Less frequent:	Increased blood creatinine, increased blood urea, acute renal failure, hyponatraemia, tubulointerstitial nephritis, nephrotic syndrome, glomerulonephritis minimal lesion, nephrolithiasis, nocturia
Reproductive system and breast disorders	
Less frequent:	Menstrual disorder
Frequency unknown:	Female infertility (female fertility decreased), vaginal haemorrhage, breast tenderness
General disorders and disorders of the administration site	
Frequent:	Influenza-like illness, peripheral oedema/fluid retention
Less frequent:	Face oedema, chest pain
Injury, poisoning and procedural complications disorders	
Frequent:	Accidental injury

Description of selected adverse reactions
In final data (adjudicated) from the APC and PreSAP trials in patients treated with celecoxib 400 mg daily for up to 3 years (pooled data from both trials), the excess rate over placebo for myocardial infarction was 7,6 events per 1 000 patients (less frequent) and there was no excess rate for stroke (types not differentiated) over placebo.

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

4.9 Overdose
There is no clinical experience of overdose. Single doses up to 1 200 mg and multiple doses up to 1 200 mg twice daily have been administered to healthy persons without significant clinical adverse effects.
In the event of a suspected overdose, appropriate supportive medical care should be provided. Dialysis is not likely to be an efficient method of medicine removal.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Category A, class 3.1 Antirheumatics (anti-inflammatory agents)
Pharmacotherapeutic group: Non-steroidal anti-inflammatory and antirheumatic drugs, NSAIDs, Coxibs, ATC code: M01AH01.
Celecoxib is a specific cyclooxygenase-2 (COX-2) inhibitor (SCI)
Cyclooxygenase-2 is induced in response to inflammatory stimuli. This leads to the synthesis and accumulation of inflammatory prostanoids, particularly prostaglandin E2, causing inflammation, oedema and pain.
Celecoxib acts as an anti-inflammatory, analgesic and anti-pyretic medicine by blocking the production of inflammatory prostanoids via COX-2 inhibition.
Celecoxib has a very low affinity for the constitutively expressed cyclooxygenase -1 enzyme (COX-1).

5.2 Pharmacokinetic properties
Absorption
When given under fasting conditions celecoxib reaches peak plasma concentrations after approximately 2-3 hours.

Celecoxib exhibits linear and dose proportional pharmacokinetics over the therapeutic dose range.
Plasma protein binding is concentration independent and is about 97 % at therapeutic plasma concentrations and the medicine is not preferentially bound to erythrocytes in the blood.

Taking a dose with food (a high fat meal) delays absorption, resulting in a Tmax of about 4 hours, and increases bioavailability by about 20 %.

Biotransformation
Celecoxib is metabolised in the liver by hydroxylation, oxidation and some glucuronidation. It was demonstrated that celecoxib is predominantly metabolised by cytochrome P450 CYP2C9. Pharmacological activity resides in the parent medicine. The main metabolites found in the circulation have no detectable COX-1 or COX-2 inhibitory activity.

Elimination
Celecoxib is mostly eliminated by hepatic metabolism with less than 1 % of the dose excreted unchanged in urine.
After multiple dosing, the elimination half-life is 8-12 hours and the rate of clearance about 500 mL/min. With multiple dosing steady state plasma concentrations are reached before day 5.
Variability among patients on the main pharmacokinetic parameters (AUC, Cmax, elimination half-life) is about 30 %. The mean steady state volume of distribution is about 500 L/70 kg in young healthy adults after a single 200 mg dose, indicating wide distribution of celecoxib into the tissues. Pre-clinical studies indicate that celecoxib crosses the blood/brain barrier.

Special populations
Hepatic impairment
Plasma concentrations of celecoxib in patients with mild hepatic impairment are not significantly different from those of age and sex matched controls.
In patients with moderate hepatic impairment celecoxib plasma concentrations are about twice those of matched controls. Patients with severe hepatic impairment have not been studied but can be expected to show accumulation of parent substance, as the main route of metabolism is via the liver.

Renal impairment
In elderly volunteers with age-related reductions in glomerular filtration rate (GFR) (mean GFR > 65 mL/min per 1,73 m2) and in patients with chronic stable renal insufficiency (GFR 35 - 60 mL/min per 1,73 m2) celecoxib pharmacokinetics were comparable to those seen in patients with normal renal function. No significant relationship was found between serum creatinine (or creatinine clearance) and celecoxib clearance.

Renal effects
The relative roles of COX-1 and COX-2 in renal physiology are not clear. **CYRETIB** reduces the urinary excretion of PGE2 and 6-keto-PGF1* (a prostacyclin metabolite) but leaves serum thromboxane B2 (TXB2) and urinary excretion of 11-dehydro-TXB2, a thromboxane metabolite (both COX-1 products) unaffected. Specific studies have shown that **CYRETIB** produces no decrease in GFR in the elderly or those with chronic renal insufficiency. These studies have also shown transient reductions in fractional excretion of sodium.

Elderly patients 65 years and older
In the population > 65 years there is a two-fold increase in mean Cmax and AUC for celecoxib. This is a predominantly weight-related rather than age-related change. Celecoxib levels are higher in lower weight individuals and therefore in the elderly population who are generally of lower mean weight than the younger population. Elderly females therefore tend to have slightly higher celecoxib plasma concentrations than elderly males.

Children
Celecoxib has not been studied in patients under 18 years old.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Capsules content
lactose monohydrate
sodium lauryl sulphate
povidone
croscarmellose sodium
magnesium stearate
Capsule shells
gelatin
titanium dioxide E171
sodium lauryl sulphate

Printing ink
shellac
propylene glycol
FD& C blue #2 aluminium lake pigment (for 100 mg capsules)
yellow iron oxide E172 (for 200 mg capsules)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
42 months

6.4 Special precautions for storage
Store at or below 25 ºC. Protect from light and moisture.
Keep the blisters in the outer carton until required for use.

6.5 Nature and contents of the container
CYRETIB 100: Transparent PVC/aluminium foil blister packs; Pack of 60 capsules.
CYRETIB 200: Transparent PVC/aluminium foil blister packs; Pack of 30 capsules.

6.6 Special precautions for disposal and other handling
Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF THE CERTIFICATES OF REGISTRATION
Trinity Pharma (Pty) Ltd
106, 16th Road
Midrand
1686
South Africa

8 REGISTRATION NUMBERS
CYRETIB 100: 49/3.1/0664
CYRETIB 200: 49/3.1/0665

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
N.A

10 DATE OF REVISION OF THE TEXT
19 October 2021

TRINITY PHARMA

SKEDULERINGSTATUS S3

1 NAAM VAN DIE MEDISYNE
CYRETIB 100, harde kapsules
CYRETIB 200, harde kapsules

2 KWALITATIEWE EN KWANTITATIEWE SAMESTELLING
Elke **CYRETIB 100** kapsule bevat 100 mg selekoksib.
Elke **CYRETIB 200** kapsule bevat 200 mg selekoksib.

Bevat suiker:

CYRETIB 100 bevat 23,525 mg laktosemonohidraat.
CYRETIB 200 bevat 47,050 mg laktosemonohidraat.
Vir 'n volledige lys van hulpstowwe, sien afdeling 6.1

3 FARMASEUTIESE VORM
Harde kapsules.
CYRETIB 100 mg kapsules is opaak, wit met blou bande op die doppie van die kapsule en wit op blou bande met die merk 100 op die agterste gedeelte van die kapsule gedruk.
CYRETIB 200 mg kapsules is opaak, wit met goue bande op die doppie van die kapsule en wit op goud bande met die merk 200 op die agterste gedeelte van die kapsule gedruk.

4 KLINIESE BESONDERHEDE
4.1 Terapeutiese indikasies
- Simptomatiese behandeling van inflammasie en pyn in osteoartritis en rumatoïede artritis
- Behandeling van pyn na tandheelkundige chirurgie.
- Behandeling van ligte tot matige post-operatiewe pyn.
- Behandeling van ligte tot matige muskuloskeletale pyn.
- Behandeling van ligte tot matige primêre dismenoree.
- Verligting van simptome van ankiloserende spondilitis.

4.2 Posologie en metode van toediening
Posologie
Aangesien die kardiovaskulêre risiko's van CYRETIB met dosis en duur van blootstelling mag toeneem, moet die laagste effektiewe daaglikse dosis gebruik word, vir die kortste moontlike duur van die behandeling.

Osteoartritis
Die aanbevole daaglikse dosering is 200 mg, geneem as 'n enkel dosering of as twee verdeelde doserings. Doserings van tot 400 mg per dag is getoets.

Rumatoïede artritis
Die aanbevole daaglikse dosering is 100 mg of 200 mg twee maal per dag.

Pyn na tandheelkundige chirurgie
Die aanbevole dosering is 100 mg tot 200 mg, tot 'n maksimum daaglikse dosering van 400 mg. Tydsverloop tussen doserings moet nie minder as 4 ure wees nie.

Ligte tot matige post-operatiewe pyn.
Die aanbevole dosering is 200 mg een keer daagliks. Sommige pasiënte mag baat vind by 'n addisionele 200 mg dosering.

Ligte tot matige muskuloskeletale pyn.
Die aanbevole dosering is 200 mg twee keer daagliks.

Ligte tot matige primêre dismenoree.
Die aanbevole dosering is 400 mg aanvanklik, gevolg deur 'n addisionele 200 mg dosering indien nodig op die eerste dag. Vir daaropvolgende dae is die aanbevole dosering 200 mg twee keer daagliks.

Ankiloserende spondilitis.
Die aanbevole daaglikse dosering is 200 mg, geneem as 'n enkeldosis of as 100 mg twee keer per dag. Sommige pasiënte mag baat by 'n totale daaglikse dosering van 400 mg.

Spesiale pasiëntgroepe
Hepatiese inkorting
Geen dosisaanpassing is nodig by pasiënte met ligte hepatiese inkorting nie. Begin **CYRETIB** met die laagste aanbevole dosis in pasiënte met matige hepatiese inkorting. Daar is geen kliniese ondervinding in pasiënte met ernstige hepatiese inkorting nie. (sien afdeling 4.3 en 5.2).

Renale inkorting
Geen dosisaanpassing is nodig by pasiënte met ligte of matige renale inkorting nie. Daar is geen kliniese ondervinding in pasiënte met ernstige renale inkorting nie. (Sien afdeling 4.3 en 5.2).

Bejaarde pasiënte
Geen dosisaanpassing is nodig nie. Alhoewel, vir bejaarde pasiënte met 'n liggaamsgewig van 50 kg of minder, is die aanbeveling om terapie te inisieer op die laagste aanbevole dosering.

Kinders
Aangesien geen data beskikbaar is nie, word **CYRETIB** nie aanbeveel vir persone jonger as 18 jaar nie.

Metode van toediening
Orale gebruik. **CYRETIB** moet heel saam met 'n glas water geneem word, met of sonder kos.

4.3 Kontraïndikasies
- Hipersensitiwiteit vir selekoksib, of enige ander hulpstof van **CYRETIB** (sien afdeling 6.1).
- Bekende hipersensitiwiteit vir sulfonamied.
- Ernstige hepatiese inkorting (serum albumien < 25 g/L of Child-Pugh telling ≥ 10).
- Ernstige renale inkorting met geskatte kreatienopruiming van < 30 mL/min.
- Asma, urtikarie, of allergiese-tipe reaksies wat deur aspirien of nie-steroïede anti-inflammatoriese middels (NSAIMs), insluitend ander siklo-oksigenase-2 (SOK-2) spesifieke inhibeerders, gepresipiteer word.
- Gevestigde iskemiese hartsiektes en/of serebrovaskulêre siektes (beroerte) en perifere arteriële siekte.
- Peri-operatiewe analgesie teen die agtergrond van koronêre arterie omleidingschirurgie (CABG).
- Aktiewe peptiese ulserasie of gastroïntestinale (GI) bloeding.
- Inflammatoriese dermsiekte.
- Tydens swangerskap en in vrouens met swangerskap-potensiaal, tensy 'n effektiewe voorbehoedmetode toegepas word (sien afdeling 4.6). Die potensiaal vir menslike risiko in swangerskap is onbekend, maar kan nie uitgesluit word nie.
- Borsvoeding (sien afdeling 4.6).

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik

CYRETIB mag predisponeer tot kardiovaskulêre insidente, serebrovaskulêre insidente, gastroïntestinale gebeure of kutaneuse reaksies, wat noodlottig mag wees.

Veiligheid en doeltreffendheid van **CYRETIB** is nog nie vasgestel vir behandeling wat langer as 12 weke in osteoartritis en 24 weke in rumatoïede artritis duur nie.

Kardiovaskulêre effekte
Verhoogde aantal ernstige kardiovaskulêre (CV) gebeure, hoofsaaklik miokardiale infarksie, is gerapporteer by pasiënte met sporadiese adenomateuse poliepe wat behandel is met selekoksib (soos in **CYRETIB**) in dosisse van 200 mg twee maal per dag en 400 mg twee maal per dag, vergeleke met placebo (sien afdeling 5.1).
Aangesien die kardiovaskulêre risiko's van **CYRETIB** kan toeneem met die dosis en blootstellingsduur, moet die kortste moontlike tydsduur en die laagste effektiewe daaglikse dosis gebruik word. NSAIMs, insluitend SOK-2-selektiewe inhibeerders, is geassosieer met 'n verhoogde risiko vir kardiovaskulêre en trombotiese newe-effekte as dit langtermyn geneem word. Die presiese omvang van die risiko verbonde aan 'n enkele dosis is nie bepaal nie, en ook nie die presiese duur van die behandeling wat verband hou met verhoogde risiko nie. Die pasiënt se behoefte aan simptomatiese verligting en reaksie op terapie moet periodiek herevalueer word, veral by pasiënte met osteoartritis (sien afdelings 4.2, 4.3, 4.8 en 5.1
Omsigtigheid word aanbeveel wanneer **CYRETIB** voorgeskryf word vir pasiënte met risiko faktore vir kardiovaskulêre insidente (bv. hipertensie, hiperlipidemie, diabetes mellitus, rook).

CYRETIB is nie 'n plaasvervanger vir asperien vir profilakse van kardiovaskulêre trombo-emboliese siektes nie weens die gebrek aan anti-plaatjie effekte. Dus, anti-plaatjie behandeling moet nie gestaak word nie.

Anafilakotoïede reaksies
Soos met NSAIMs in die algemeen, het anafilakotoïede reaksies voorgekom by pasiënte wat aan **CYRETIB** blootgestel is (sien afdeling 4.3).

Gastroïntestinale (GI) effekte
Boonste en onderste gastroïntestinale komplikasies (perforasies, ulkusse of bloeding (PUBs)), waarvan sommige noodlottig was, het voorgekom by pasiënte wat met selekoksib (soos in **CYRETIB**) behandel was. Omsigtigheid word aanbeveel met die behandeling van pasiënte met die grootste risiko om gastroïntestinale komplikasies met NSAIMs te ontwikkel; bejaardes, pasiënte wat enige ander NSAIMs of anti-plaatjie medisyne (soos asperien) of glukokortikoïede gelyktydig gebruik, pasiënte wat alkohol gebruik, of pasiënte met 'n voorafgaande geskiedenis van gastroïntestinale siekte, soos ulserasie en GI bloeding.

Wanneer **CYRETIB** saam met aspirien geneem word (selfs teen lae dosisse), is daar 'n verdere toename in die risiko van gastroïntestinale newe-effekte vir selekoksib (gastroïntestinale ulserasie of ander gastroïntestinale komplikasies).

'n Beduidende verskil in GI-veiligheid tussen selektiewe SOK-2 inhibeerders plus aspirien teenoor NSAIMs plus aspirien is nie in langtermyn kliniese toetse getoon nie.

Gelyktydige NSAIM gebruik
Die gelyktydige gebruik van **CYRETIB** en 'n nie-aspirien NSAIM moet vermy word.

Vloeistofretensie en edeem
Vloeistofretensie en edeem is waargeneem by pasiënte wat selekoksib (soos in **CYRETIB**) gebruik het. Dus, moet **CYRETIB** met sorg gebruik word by pasiënte met 'n geskiedenis van hartversaking, linker ventrikulêre disfunksie of hipertensie, en by pasiënte met bestaande edeem vanweë enige ander rede, aangesien prostaglandien-inhibisie kan lei tot verswakking van die nierfunksie en vloeistofretensie.

Omsigtigheid is ook nodig by pasiënte wat diuretika behandeling neem of risiko van hipovolemie het.

Pasiënte met voorafbestaande kongestiewe hartversaking of hipertensie moet noukeurig gemonitor word.

Hipertensie
NSAIMs, insluitend selekoksib (soos in **CYRETIB**) mag lei tot die aanvang van nuwe hipertensie of verergering van voorafbestaande hipertensie, wat albei kan bydra tot die verhoogde voorkoms van kardiovaskulêre insidente. Daarom moet bloeddruk noukeurig monitor word tydens die aanvang van die behandeling met **CYRETIB** en gedurende die verloop van die behandeling.

Hepatiese en renale effekte
Verswakte renale of hepatiese funksie en veral kardiale disfunksie is meer algemeen by bejaardes en daarom moet medies gepaste toesig gehandhaaf word.

NSAIMs, insluitend **CYRETIB**, mag renale toksisiteit veroorsaak. Selekoksib het renale effekte getoon soortgelyk aan die waargeneem by vergelykende NSAIMs. Pasiënte met die grootste risiko vir renale toksisiteit is diegene met verswakte renale funksie, hartversaking, lewer disfunksie, en diegene wat diuretika, angiotensienomskakelende ensiem (AOE)-inhibeerders, angiotensien II reseptor antagoniste gebruik en bejaardes (sien afdeling 4.5). Sulke pasiënte moet noukeurig gemonitor word tydens behandeling met **CYRETIB**.

Sommige gevalle van ernstige hepatiese reaksies, insluitend fulminante hepatitis (sommige met noodlottige uitkoms), lewernekrose en hepatiese inkorting (sommige met noodlottige uitkoms of vereiste leweroorplanting), is aangemeld met selekoksib (vervat in **CYRETIB**). Onder die gevalle wat die tyd tot aanvang gerapporteer het, het meeste van die ernstige hepatiese newe-effekte ontwikkel binne een maand na die aanvang van selekoksib (vervat in **CYRETIB**) behandeling (sien afdeling 4.8).

As pasiënte tydens behandeling verswak in enige van die bogenoemde orgaanstelsel funksies, moet toepaslike maatreëls getref word en staking van die **CYRETIB** terapie oorweeg word.

Omsigtigheid moet aan die dag gelê word as behandeling begin word by pasiënte met dehidrasie. Dit is raadsaam om pasiënte eers te rehidreer en dan terapie met **CYRETIB** te begin.

CYP2D6 inhibasie
Selekoksib inhibeer CYP2D6. Alhoewel dit nie 'n sterk inhibeerder van die ensiem is nie, mag 'n dosisverlaging van **CYRETIB** noodsaaklik wees vir individuele dosis-getitreerde medisyne wat gemetaboliseer word deur CYP2D6 (sien afdeling 4.5).

CYP2C9 swak metaboliseerders
Pasiënte wat bekend is dat hulle CYP2C9 swak metaboliseerders is, moet met sorg behandel word.

Vel en sistemiese hipersensitiwiteitsreaksies
Ernstige vel reaksies, sommige noodlottig, insluitend eksfoliatiewe dermatitis, Steven-Johnson sindroom, en toksiese epidermale nekrolise is in baie seldsame gevalle in assosiasie met die gebruik van selekoksib (soos in **CYRETIB**) aangemeld, sien afdeling 4.8.

Pasiënte blyk die grootste risiko vir hierdie gebeure te hê vroeg in die loop van die behandeling: die aanvang van die gebeurtenis kom in die meeste gevalle binne die eerste maand van die behandeling voor. Ernstige hipersensitiwiteitsreaksies (insluitend anafilakse, angio-edeem en geneesmiddeluitslag met eosinofilie en sistemiese simptome (DRESS) of hipersensitiwiteitsindroom) is gerapporteer by pasiënte wat selekoksib (soos in **CYRETIB**) ontvang het, sien afdeling 4.8.
Pasiënte met 'n geskiedenis van sulfonamied-allergie of enige geneesmiddel-allergie, mag 'n groter risiko hê vir ernstige velreaksies of hipersensitiwiteitsreaksies (sien afdeling 4.3). **CYRETIB** moet gestaak word met die eerste verskyning van veluitslag, slymvliesletsels, of enige ander teken van hipersensitiwiteit.

Algemeen
CYRETIB kan koors en ander tekens van inflammasie maskeer.

Gebruik saam orale antikoagulante
By pasiënte op gelyktydige behandeling met warfarien, is ernstige bloedingsinsidente, waarvan sommige noodlottig was, gerapporteer (sien afdelings 4.8 en 4.5). Omdat 'n toename in protrombientyd (INR) aangemeld is, moet antikoagulerende aktiwiteit noukeurig gemonitor word by pasiënte wat warfarien/kumarien-tipe orale antikoagulante ontvang, veral wanneer behandeling met **CYRETIB** geïnisieer word, of die dosis daarvan verander word (sien afdeling 4.5) . Gelyktydige gebruik van antikoagulante met NSAIMs kan die risiko van bloeding verhoog. Omsigtigheid moet aan die dag gelê word wanneer **CYRETIB** gekombineer word met warfarien of ander orale antikoagulante, insluitend nuwe antistolmiddels (bv. apiksabaan, dabigatran en rivaroksabaan).

Hulpstowwe
CYRETIB 100 mg en 200 mg kapsules bevat laktosemonohidraat (sien afdelings 2 en 6.1). Pasiënte met seldsame oorerflike probleme van galaktose-onverdraagsaamheid, totale laktase-gebrek of glukose/galaktose-wanabsorpsie moet nie **CYRETIB** neem nie.

4.5 Interaksie met ander medisyne en ander vorms van interaksie
Farmakodinamiese interaksies
Antikoagulante
By pasiënte wat op gelyktydige behandeling met warfarien is, is toenames in protrombientyd (INR) aangemeld (sien afdeling 4.4).
Antikoagulant aktiwiteit moet gemonitor word, veral in die eerste paar dae na inisiëring of verandering van die dosis van **CYRETIB** in pasiënte wat warfarien of ander antikoagulante ontvang aangesien hierdie pasiënte 'n verhoogde risiko van bloeding komplikasies het. Dus, pasiënte wat orale antikoagulante ontvang, moet noukeurig gemonitor word vir protrombientyd INR, veral in die eerste paar dae wanneer **CYRETIB** behandeling geïnisieer word of as die dosis verander word (sien afdeling 4.4). Bloedingsgevalle geassosieer met verhoogde protrombientyd (INR) is gerapporteer by pasiënte (hoofsaaklik by bejaardes) wat selekoksib (soos in **CYRETIB**) gelyktydig met warfarien ontvang, sommige gevalle noodlottig van aard.

Antihipertensiewe middels
NSAIMs, insluitend **CYRETIB**, mag die effek van antihipertensiewe medisyne (insluitend AOE inhibeerders, angiotensien II reseptorantagoniste, diuretika en beta-blokkeerders) verminder. Hierdie interaksie moet oorweeg word by pasiënte wat **CYRETIB** saam met antihipertensiewe medisyne gebruik.

Wat NSAIMs betref, mag die risiko van akute renale inkorting, wat gewoonlik omkeerbaar is, verhoog word by sommige pasiënte met gekompromitteerde renale funksie (bv. gedehidreerde pasiënte, pasiënte met diuretika of bejaarde pasiënte) wanneer AOE inhibeerders of angiotensien II reseptorantagoniste, en/of diuretika gekombineer word met NSAIMs, insluitend **CYRETIB** (sien afdeling 4.4). Dus, moet die kombinasie met omsigtigheid toegedien word, veral by bejaardes. Pasiënte moet voldoende gehidreer word en daar moet oorweeg word om die renale funksie te monitor na die aanvang van die gelyktydige behandeling asook periodies daarna.

Kliniese studies, sowel as waarnemings ná bemarking, het getoon dat NSAIMs die natriuretiese effek van furosemied en tiasiede by sommige pasiënte kan verminder. Hierdie reaksie word toegeskryf aan die inhibisie van renale prostaglandien sintese.

Siklosporien en takrolimus
Gelyktydige toediening van NSAIMs (insluitend **CYRETIB**) en siklosporien of takrolimus kan die nefrotoksiese effek van onderskeidelik siklosporien of takrolimus verhoog. Renale funksie moet gemoniteer word wanneer **CYRETIB** en enige van hierdie medisyne gekombineer word.

Aspirien
CYRETIB mag saam met lae-dosis aspirien gebruik word. Alhoewel gelyktydige toediening van aspirien met **CYRETIB** mag lei tot 'n verhoogde voorkoms van GI ulserasie of ander komplikasies, vergeleke met die gebruik van **CYRETIB** alleen. Vanweë die gebrek aan plaatjie-effekte, is **CYRETIB** nie 'n plaasvervanger van aspirien vir kardiovaskulêre profilakse nie.

Daar is geen bestendige bewyse dat gelyktydige gebruik van aspirien die verhoogde risiko vir ernstige kardiovaskulêre trombotiese insidente wat geassosieerd is met **CYRETIB** verminder nie.

'n Verhoogde risiko vir gastro-intestinale ulserasie of ander gastro-intestinale komplikasies in vergelyking met die gebruik van **CYRETIB** alleen is getoon vir gelyktydige toediening van lae-dosis aspirien.

Farmakokinetiese interaksies
*Effekte van **CYRETIB** op ander medisyne*
CYP2D6 inhibisie
Selekoksib is 'n inhibeerder van CYP2D6. Die plasmakonsentrasies van medisyne wat substrate van hierdie ensiem is, kan verhoog word wanneer **CYRETIB** gelyktydig gebruik word. Voorbeelde van medisyne wat deur CYP2D6 gemetaboliseer word, is antidepressante (trisikliese en SSRI's), neuroleptika, anti-disritmiese medisyne, ens. Die dosis van individuele dosis-getitreerde CYP2D6 substrate moet moontlik verminder word wanneer behandeling met **CYRETIB** geïnisieer word, of verhoog word indien behandeling met **CYRETIB** gestaak word.

Gelyktydige toediening van selekoksib 200 mg twee maal per dag het gelei tot 2,6-voudige en 1,5-voudige toenames in plasmakonsentrasies van dekstrometorfaan en metoprolol (CYP2D6 substrate) onderskeidelik. Hierdie verhogings is as gevolg van selekoksib CYP2D6 inhibisie van die CYP2D6 substraatmetabolisme.

CYP2C19 inhibisie
In vitro studies het 'n mate van potensiaal getoon vir selekoksib om die CYP2C19-gekataliseerde metabolisme te inhibeer. Die kliniese belang van hierdie in vitro bevinding is onbekend. Voorbeelde van medisyne wat deur CYP2C19 gemetaboliseer word, is diasepien, sitalopraam en imipramien.

Metotreksaat
By pasiënte met rumatoïede artritis het selekoksib geen statisties beduidende effek op die farmakokinetika (plasma- of renale klaring) van metotreksaat (in rumatologiese dosisse) gehad nie. Alhoewel, voldoende monitering vir metotreksaat-verwante toksisiteit oorweeg moet word wanneer hierdie twee medisyne gekombineer word.

Litium
By gesonde persone, het die gelyktydige toediening van selekoksib 200 mg twee maal per dag met 450 mg litium twee maal per dag gelei tot 'n gemiddelde toename in Cmaks van 16 % en in die area onder die kurwe (AOK) van 18 % vir litium. Dus, pasiënte op litium behandeling moet noukeurig gemonitor word wanneer **CYRETIB** begin of onttrek word.

Orale voorbehoedmiddels
In 'n interaksie studie het selekoksib geen klinies relevante uitwerking op die farmakokinetika van orale voorbehoedmiddels (1 mg noretinderoon/35 mikrogram etinielestradiol), gehad nie.

Glibenklamied/tolbutamied
Selekoksib beïnvloed nie die farmakokinetika van tolbutamied (CYP2C9 substraat) of glibenklamied in 'n klinies beduidende mate nie.

Fenitoïen
In spesifieke studies by gesonde vrywilligers met ander medisyne wat deur CYP2C9 gemetaboliseer is, is gevind dat selekoksib geen klinies beduidende farmakokinetiese interaksie met fenitoïen lewer nie.

*Effekte van ander medisyne op **CYRETIB***
CYP2C9 swak metaboliseerders
By individue waar CYP2C9 swak metaboliseerders is en verhoogde sistemiese blootstelling aan selekoksib toon, kan gelyktydige behandeling met CYP2C9 inhibeerders soos flukonasool lei tot verdere toename in selekoksib blootstelling. Sulke kombinasies moet vermy word by bekende CYP2C9 swak metaboliseerders (sien afdeling 4.4).

CYP2C9 inhibeerders en induseerders
Aangesien selekoksib hoofsaaklik deur CYP2C9 gemetaboliseer word, moet **CYRETIB** teen die helfte van die aanbevole dosis gebruik word by pasiënte wat flukonasool ontvang. Gelyktydige toediening van 200 mg enkele dosis selekoksib en 200 mg een maal per dag flukonasool, 'n kragtige CYP2C9 inhibeerder, het gelei tot 'n gemiddelde toename in selekoksib Cmaks van 60 % en in AOK van 130 %. Gelyktydige gebruik van induseerders van CYP2C9 soos rifampisien, karbaamasepien en barbiturate kan die plasmakonsentrasie van selekoksib verlaag.

Ketokonasool en teensuurmiddels
Daar is nie waargeneem dat ketokonasool of teensuurmiddels die farmakokinetika van selekoksib beïnvloed nie.

Pediatriese bevolkingsgroepe
Interaksiestudies is slegs by volwassenes uitgevoer.

4.6 Vrugbaarheid, swangerskap en borsvoeding
Swangerskap
CYRETIB is gekontraïndikeerd tydens swangerskap (sien afdeling 4.3)
CYRETIB kan uteriene traagheid en premature sluiting van die ductus arteriosus veroorsaak en moet tydens swangerskap vermy word.

Borsvoeding
Beperkte data dui aan dat **CYRETIB** in borsmelk uitgeskei word en moet dus nie gebruik word tydens laktasie nie.

Vrugbaarheid
Op grond van die meganisme van werking, kan die gebruik van NSAIMs, insluitend **CYRETIB**, die skeuring van ovariale follikels vertraag of verhoed, wat geassosieer word met omkeerbare onvrugbaarheid in sommige vroue.

4.7 Uitwerking op die vermoë om te bestuur en masjiene te gebruik
Die effek van selekoksib op die vermoë om te bestuur of masjinerie te hanteer, is nie bestudeer nie, maar op grond van die farmakodinamiese eienskappe en die algehele veiligheidsprofiel, is dit onwaarskynlik dat dit 'n uitwerking sal het. Pasiënte wat duiseligheid, vertigo of lomerigheid ervaar (sien afdeling 4.8) tydens gebruik van **CYRETIB**, moet hulle weerhou om te bestuur of masjinerie te hanteer.

4.8 Newe-effekte
Getabuleerde opsomming van newe-effekte

Infeksies en infestasies	
Gereeld:	Sinusitis, boonste lugweginfeksie, faringitis, urienweginfeksie, brongitis
Minder gereeld:	Helicobacter infeksie, herpes zoster, erisipelas, brongopneumonie, labirintitis, tandvleisinfeksie
Bloed- en Limfatiese Sisteemversteurings	
Minder gereeld:	Anemie, leukopenie, trombositopenie, pansitopenie, agranulositose, eggimose
Immuunstelselversteurings	
Gereeld:	Hipersensitiwiteit, verergering van allergie
Minder gereeld:	Anafilaktiese skok, anafilaktiese reaksie, angio-edeem
Frekwensie onbekend:	Anafilaksis
Metabolisme- en voedingsversteurings	
Gereeld:	Gewigstoename
Minder gereeld:	Hiperkalemie, verhoogde bloed natrium
Psigiatriese versteurings	
Gereeld:	Slaaploosheid
Minder gereeld:	Angs, depressie, moegheid, konfusie, hallusinasies
Senusisteemversteurings	
Gereeld:	Duiseligheid, hipertonie, hoofpyn
Frekwensie onbekend:	Serebrale infarksie (beroerte), para-estesie, lomerigheid, ataksie, disgeusie, intrakraniale bloeding (insluitend noodlottige intrakraniale bloeding), aseptiese meningitis, epilepsie (insluitend verergerende epilepsie), ageusie, anosmie
Oogversteurings	
Minder gereeld:	Dowwe visie, konjunktivitis, oog bloeding, retinale arterie-okklusie, retinale aar-okklusie, glasagtige drywers, konjunktiewe bloeding
Oor- en doolhofversteurings	
Minder gereeld:	Tinnitus, hipoakusie, disfonie
Kardiale versteurings	
Gereeld:	Miokardiale infarksie, angina pectoris
Minder gereeld:	Hartversaking, palpitasie, tagikardie, disritmie
Frekwensie onbekend:	Kardiovaskulêre trombotiese insidente
Vaskulêre versteurings	
Gereeld:	Hipertensie (insluitend verergerende hipertensie)
Minder gereeld:	Pulmonêre embolisme, blosing, vaskulitis, diep veneuse trombose
Respiratories-, torakale- en mediastinale versteurings	
Gereeld:	Rinitis, hoes, dispnee
Minder gereeld:	Brongospasma, pneumonitis
Gastroïntestinale versteurings	
Gereeld:	Naarheid, abdominale pyn, diarree, dispepsie, winderigheid, braking, disfagie, prikkelbare dermsindroom, tandsiekte
Minder gereeld:	Konstipasie, gastritis, stomatitis, gastroïntestinale inflammasie (insluitend verergerende gastroïntestinale inflammasie), eruktasie, gastroïntestinale bloeding, duodenale ulkus, gastriese ulkus, esofageale ulkus, intestinale ulkus, dikderm ulkus, intestinale perforasie, esofagitis, melena, pankreatitis, kolitis, aambei bloeding, gereelde ontlasting, mond ulserasie
Hepato-biliêre versteurings	
Minder gereeld:	Abnormale hepatiese funksie, verhoogde hepatiese ensieme (insluitend verhoogde AST en ALT), hepatitis, leweversaking (soms noodlottig of vereiste leweroorplanting), fulminante hepatitis (sommige met noodlottige uitkoms), hepatiese nekrose, cholestase, cholestatiese geelsug
Vel- en Onderhuidse weefselversteurings	
Gereeld:	Uitslag, pruritus (insluitend veralgemeende pruritus)
Minder gereeld:	Urtikarie, eggimose, alopesie, fotosensitiwiteit, eksfoliatiewe dermatitis, eritematiese multiforme, Stevens-Johnson sindroom, toksiese epidermale nekrolise, medisyne uitslag met eosinofilie en sistemiese simptome (DRESS), akute algemene eksantematiese pustulose (AGEP), bulleuse dermatitis, lipoom, allergiese dermatitis, ganglion
Muskuloskeletale bindweefselversteurings	
Gereeld:	Artralgie
Minder gereeld:	Spier spasmas (spierkrampe), miositis, onderste ledemaat frakture
Nier- en urienweg afwykings	
Minder gereeld:	Verhoogde bloed kreatien, verhoogde bloedureum, akute renale versaking, hiponatremie, tubulêre-interstisiële nefritis, nefrotiese sindroom, glomerulonefritis minimale letsel, nefrolitiase, nokturie
Voortplantingstelsel- en borsafwykings	
Minder gereeld:	Menstruele afwykings
Frekwensie onbekend:	Vroulike onvrugbaarheid (verlaagde vroulike vrugbaarheid), vaginale bloeding, bors teerheid
Algemene siektes en toedieningsarea toestande	
Gereeld:	Griepagtige simptome, perifere edeem/vloeistof retensie
Minder gereeld:	Gesig edeem, bors pyn
Beserings, vergiftiging en prosedurele komplikasies versteurings	
Gereeld:	Beserings wat per ongeluk gebeur

Beskrywing van geselekteerde newe-effekte
In finale data (beoordeel) uit die APC en PreSAP proewe by pasiënte behandel met selekoksib 400 mg daagliks vir tot en met 3 jaar (saamgevoegde data uit albei proewe), was die oortolligheidskoers bo placebo vir miokardiale infarksie 7,6 insidente per 1 000 pasiënte (minder gereeld) en daar was geen oortolligheidskoers vir beroerte (tipes nie gedifferensieerd nie) oor placebo.

Rapportering van vermoedelike newe-effekte
Dit is belangrik om vermoedelike newe-effekte wat waargeneem word nadat die medisyne goedgekeur is, te rapporteer. Dit laat volgehoue observasie van die voordeel/risiko-balans van die medisyne toe. Gesondheidsorgverskaffers word versoek om enige vermoedelike newe-effekte aan SAHPRA te rapporteer via die "6.04 Adverse Drug Reactions Reporting Form", wat aanlyn by SAHPRA se publikasies gevind kan word: https://www.sahpra.org.za/Publications/Index/8

4.9 Oordosering
Daar is geen kliniese ondervinding ervaring oordosering nie. Enkele dosisse van so veel as 1 200 mg en veelvuldige dosisse van tot 1 200 mg twee maal per dag is al toegedien aan gesonde persone sonder beduidende kliniese nadelige uitwerkings.
In geval van 'n vermoedelike oordosering, moet geskikte ondersteunende mediese sorg verskaf word.
Dialise is waarskynlik nie 'n doeltreffende metode van geneesmiddel verwydering nie.

5 FARMAKOLOGIESE EIENSKAPPE
5.1 Farmakodinamiese eienskappe
Kategorie A, klas 3.1 Rumatiekmiddels (anti-inflammatoriese middels)
Farmakoterapeutiese groep: Nie-steroïdale anti-inflammatoriese en antirumaties middels, NSAIMs, SOKs, ATC kode: M01AH01.
Selekoksib is 'n spesifieke siklo-oksigenase-2 (SOK-2) inhibeerder (SSI)
Siklo-oksigenase-2 word geïnduseer in reaksie op inflammatoriese prikkels. Dit lei tot die sintese en ophoping van inflammatoriese prostanoïede, veral prostaglandien E2, wat inflammasie, edeem en pyn veroorsaak.
Selekoksib tree as 'n anti-inflammatoriese, pynstillende en koorswerende middel op deurdat dit die produksie van inflammatoriese prostanoïede deur middel van SOK-2 inhibisie blokkeer.
Selekoksib het 'n baie lae affiniteit vir die konstituerende uitgedrukte siklo-oksigenase -1 ensiem (SOK-1).

5.2 Farmakokinetiese eienskappe
Absorpsie
Wanneer selekoksib onder vastende toestande toegedien word, word piek plasma konsentrasies bereik na ongeveer 2-3 ure.

Selekoksib toon liniêre, en dosis-proporsionele farmakokinetika oor die terapeutiese dosis reikwydte.
Plasmaproteïenbinding is konsentrasie-afhanklik en is ongeveer 97 % by terapeutiese plasma konsentrasies, en die geneesmiddel word nie by voorkeur aan eritrosiete in die bloed gebind nie.

Dosering saam met voedsel ('n hoë-vet maaltyd) verlaag absorpsie en veroorsaak 'n Tmaks van ongeveer 4 uur, en verhoog biobeskikbaarheid met ongeveer 20 %.

Biotransformasie
Selekoksib word in die lewer gemetaboliseer deur hidroksilering, oksidasie en 'n mate van glukuronidasie. Daar is aangetoon dat selekoksib hoofsaaklik gemetaboliseer word deur sitochroom P450 CYP2C9. Farmakologiese aktiwiteit berus in die stamverbinding. Die hoof metaboliete wat in die sirkulasie aangetref word, het geen opmerkbare SOK-1 of SOK-2 inhibeerder aktiwiteit nie.

Eliminasie
Selekoksib word hoofsaaklik geëlimineer deure hepatiese metabolisme met minder as 1 % van die dosis wat onveranderd in die urine uitgeskei word.
Na veelvuldige doserings, is die eliminasie halfleeftyd 8-12 ure en die tempo van opruiming ongeveer 500 mL/min. Met veelvuldige dosering word gelykvlak-plasmakonsentrasies bereik voor dag 5.
Variasie tussen pasiënte met betrekking tot die hoof farmakokinetiese parameters (AOK, Cmaks, eliminasie halfleeftyd) is ongeveer 30 %. Die gemiddelde gelykvlak-verspreidingsvolume is ongeveer 500 L/70 kg in jong, gesonde volwassenes na 'n enkel 200 mg dosis, wat aandui dat selekoksib wyd in die weefsel versprei word. Pre-kliniese studies toon dat selekoksib oor die bloed-brein-skans beweeg.

Spesiale pasiëntgroepe
Hepatiese inkorting
Plasma konsentrasies van selekoksib in pasiënte met ligte hepatiese inkorting verskil nie beduidend van dié van ouderdoms- en geslagsgebaseerde kontroles nie.
In pasiënte met matige hepatiese inkorting is plasmakonsentrasies van selekoksib ongeveer twee keer so hoog as dié van ooreenstemmende kontroles.
Pasiënte met ernstige hepatiese inkorting is nog nie bestudeer nie, maar dit kan verwag word dat hulle ophoping van die stamverbinding sal toon, omdat die lewer die hoofstelsel van metabolisme is.

Renale inkorting
In bejaarde vrywilligers met ouderdomsverwante verlagings in glomerulêre filtrasie spoed (GFS) (gemiddelde GFS > 65 mL/min per 1,73 m2) en in pasiënte met kroniese stabiele renale ontoereikendheid (GFR 35 - 60 mL/min per 1,73 m2), was selekoksib farmakokinetika vergelykbaar met dié wat in die pasiënte met normale renale funksie waargeneem is. Geen beduidende verwantskap tussen serumkreatinien (of kreatinienopruiming) en selekoksib opruiming is vasgestel nie.

Renale effekte
Die relatiewe rolle van SOK-1 en SOK-2 in renale fisiologie is nog onduidelik.
CYRETIB verminder die urinêre uitskeiding van PGE2 en 6-keto-PGF1* ('n prostasiklien metaboliet), maar beïnvloed nie serum-tromboksaan B2 (TXB2) en die urinêre uitskeiding van 11-dehydro-TXB2, 'n tromboksaan metaboliet (albei SOK-1 produkte) nie. Spesifieke studies het aangedui dat **CYRETIB** geen verlagings in GFS in bejaardes en in persone met kroniese renale ontoereikendheid veroorsaak nie. Hierdie studies het ook verbygaande verlagings in fraksionele uitskeiding van natrium aangedui.

Bejaarde pasiënte 65 jaar en ouer
In die populasie > 65 jaar is daar 'n tweevoudige toename in gemiddelde Cmaks en AOK vir selekoksib. Dit is 'n oorwegend gewigsverwante eerder as ouderdomsverwante verandering. Selekoksib-vlakke is hoër in laer gewig individue en dus in die ouer bevolking wat gewoonlik 'n laer gemiddelde gewig het as die jonger bevolking. Bejaarde vroue is dus geneig om effens hoër plasmakonsentrasies van selekoksib te hê as bejaarde mans.

Pediatriese pasiëntgroepe
Selekoksib is nie bestudeer by pasiënte jonger as 18 jaar nie.

6 FARMSEUTIESE BESONDERHEDE
6.1 Lys van hulpstowwe
Kapsule inhoud
laktosemonohidraat
natriumlaurielsulfaat
povidoon
natriumkroskarmellose
magnesiumstearaat
Dop van kapsule
gelatien
titaandioksied E171
natriumlaurielsulfaat

Drukink
skilferlak
propileenglikool
FD& C blou #2 aluminium lake pigment (vir 100 mg kapsules)
geel ysteroksied E172 (vir 200 mg kapsules)

6.2 Onverenigbaarheid
Nie van toepassing.

6.3 Rakleeftyd
42 maande

6.4 Spesiale voorsorgmaatreëls tydens berging
Bêre teen of benede 25 °C. Beskerm teen lig en vog.
Hou die stolpverpakking in die buiteste karton totdat dit benodig word vir gebruik.

6.5 Aard en inhoud van die houer
CYRETIB 100: Deursigtige PVC/aluminiumfoelie stolpverpakking; Pak van 60 kapsules.
CYRETIB 200: Deursigtige PVC/aluminiumfoelie stolpverpakking; Pak van 30 kapsules.

6.6 Spesiale voorsorgmaatreëls vir wegdoening en ander hantering
Enige ongebruikte produk of afvalmateriaal moet teruggeneem word na die apteker vir veilige wegdoening, in ooreenstemming met plaaslike vereistes.

7 HOUER VAN REGISTRASIESERTIFIKAAT
Trinity Pharma (Pty) Ltd
106, 16de Weg
Midrand
1686
Suid-Afrika

8 REGISTRASIENOMMER(S)
CYRETIB 100: 49/3.1/0664
CYRETIB 200: 49/3.1/0665

9 DATUM VAN EERSTE MAGTIGING / HERNUWING VAN DIE MAGTIGING
N.A

10 DATUM VAN HERSIENING VAN DIE TEKS
19 Oktober 2021