SCHEDULING STATUS S3

1 NAME OF THE MEDICINE

INNOFLAM 100, hard capsules

INNOFLAM 200, hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **INNOFLAM** 100 capsule contains 100 mg celecoxib.

Each **INNOFLAM** 200 capsule contains 200 mg celecoxib.

Excipient with known effect

Contains sugar: Lactose monohydrate

Each **INNOFLAM** 100 capsule contains 25 mg of lactose monohydrate

Each **INNOFLAM** 200 capsule contains 50 mg of lactose monohydrate

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Hard gelatin capsules.

(PRODUCT NAME) 100: Hard gelatin capsules size “3” having imprinting “135” on the opaque white body with blue ink and “A” on the opaque white cap with blue ink filled with white to off white colored granular powder.

(PRODUCT NAME) 200: Hard gelatin capsules size “1” having imprinting “136” on the opaque white body with golden yellow ink and “A” on the opaque white cap with

golden yellow ink filled with white to off white colored granular powder.

4 CLINICAL PARTICULARS

4.1 Indications

- Symptomatic treatment of inflammation and pain in osteoarthritis and rheumatoid arthritis.
- Treatment of pain after 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 INNOFLAM 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 **INNOFLAM** 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, **INNOFLAM** is not recommended in persons under 18 years old.

Method of administration

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

4.3 Contraindications

- Hypersensitivity to celecoxib, or any other excipient of **INNOFLAM** (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

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

Safety and efficacy of **INNOFLAM** 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 **INNOFLAM**) at doses of 200 mg twice daily and 400 mg twice daily, compared to placebo (see section 5.1).

As the cardiovascular risks of **INNOFLAM** 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 **INNOFLAM** is prescribed to patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

INNOFLAM 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 **INNOFLAM** (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 **INNOFLAM**). 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 **INNOFLAM** 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 **INNOFLAM** 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 **INNOFLAM**). Therefore, **INNOFLAM** 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 **INNOFLAM**) 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 **INNOFLAM** 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 **INNOFLAM**, 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 **INNOFLAM**.

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 **INNOFLAM**. 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 **INNOFLAM** 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 **INNOFLAM** 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 **INNOFLAM** therapy.

CYP2D6 inhibition

Celecoxib inhibits CYP2D6. Although it is not a strong inhibitor of this enzyme, a dose reduction of **INNOFLAM** 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 **INNOFLAM**), 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 **INNOFLAM**), 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). **INNOFLAM** should be discontinued at the first appearance of skin rash, mucosal lesions, or any other

sign of hypersensitivity.

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

General

INNOFLAM 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 **INNOFLAM** 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 **INNOFLAM** with warfarin or other oral anticoagulants, including novel anticoagulants (e.g. apixaban, dabigatran, and rivaroxaban).

Excipients

INNOFLAM 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 **INNOFLAM**.

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 **INNOFLAM** 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 **INNOFLAM** 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 **INNOFLAM**) concurrently with warfarin, some of them fatal.

Anti-hypertensives

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

Aspirin

INNOFLAM can be used with low-dose aspirin. However, concomitant administration of aspirin with **INNOFLAM** may result in an increased rate of GI ulceration or other complications, compared to use of **INNOFLAM** alone. Because of its lack of platelet effects, **INNOFLAM** 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 **INNOFLAM**.

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

Pharmacokinetic interactions

*Effects of **INNOFLAM** 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 **INNOFLAM** 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 **INNOFLAM** is initiated or increased if treatment with **INNOFLAM** 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 C_{max} of 16 % and in area under the curve (AUC) of 18 % of lithium. Therefore, patients on lithium treatment should be closely monitored when **INNOFLAM** 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 **INNOFLAM***

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, **INNOFLAM** 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 C_{max} 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

INNOFLAM is contraindicated in pregnancy (see section 4.3)

INNOFLAM may cause uterine inertia and premature closure of the ductus arteriosus and should be avoided during pregnancy.

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.

The use of **INNOFLAM** should be limited to the lowest effective dose for the shortest duration, if deemed necessary by a healthcare professional. (see section 4.3 and 4.4)

Breastfeeding

Limited data indicate that **INNOFLAM** 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 **INNOFLAM**, 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

Patients who experience dizziness, vertigo or somnolence (see section 4.8) while taking **INNOFLAM** 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.

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) [see Section 4.4]

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 T_{max} 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, C_{max}, 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 m^2) and in patients with chronic stable renal insufficiency (GFR 35 - 60 mL/min per 1,73 m^2) 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. **INNOFLAM** reduces the urinary excretion of PGE_2 and 6-keto-PGF1$\propto$ (a prostacyclin metabolite) but leaves serum thromboxane B_2 (TXB_2) and urinary excretion of 11-dehydro-TXB_2, a thromboxane metabolite (both COX-1 products) unaffected. Specific studies have shown that **INNOFLAM** 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 C_{max} 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

(PRODUCT NAME) 100 AND 200

Croscarmellose sodium, FD & C blue # 2 aluminum lake, gelatin, lactose monohydrate, magnesium stearate, povidone, purified water, shellac, sodium lauryl sulfate, titanium dioxide E 171, yellow iron oxide

6.2 Incompatibilities

None

6.3 Shelf life

36 months from manufacturing date

6.4 Special precautions for storage

Store at or below 30 °C in original container to protect from moisture.

6.5 Nature and contents of the container

(PRODUCT NAME) 100 and 200 is available in

- (10's, 20, 30's & 60's) blisters of unprinted aluminum foil & unprinted CFB foil in one carton. In pack sizes of multiples of 10 capsules per blister.
- (10's, 20's,30's &60's) blisters of plain aluminum foil & plain OPA/ALU/PVC CFB foil in one carton. In pack sizes of multiples of 10 capsules per blister.
- (10's, 20's, 30's & 60's) blisters of plain aluminum foil & transparent PVC/PE/PVDC film in one carton. In pack sizes of multiples of 10 capsules per blister.

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

Innovata Pharmaceuticals (Pty) LTD

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

2091

South Africa

8 REGISTRATION NUMBERS

INNOFLAM 100: A 51/3.1/0722

INNOFLAM 200: A 51/3.1/0723

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 September 2021

10 DATE OF REVISION OF THE TEXT