PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

CELECOXIB 100 ASCENDIS hard gelatin capsules

CELECOXIB 200 ASCENDIS hard gelatin capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CELECOXIB 100 ASCENDIS capsule contains 100 mg celecoxib.

Contains sugar (lactose as lactose monohydrate 27,07 mg per capsule).

Each CELECOXIB 200 ASCENDIS capsule contains 200 mg celecoxib.

Contains sugar (lactose as lactose monohydrate 54,14 mg per capsule).

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Hard gelatin capsules

CELECOXIB 100 ASCENDIS: Size “2” capsules opaque white with a blue band reverse printed “100” in white on body and “CEL” in white on cap.

CELECOXIB 200 ASCENDIS: Size “2” capsules opaque white with a yellow band reverse printed “200” in white on body and “CEL” in white on cap.

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 signs and symptoms of ankylosing spondylitis.

4.2 Posology and method of administration

Posology

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

Osteoarthritis

The recommended daily dose is 200 mg, administered as a single dose or as two divided doses. A maximum dose is 400 mg per day.

Rheumatoid arthritis

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

Pain post dental surgery

The recommended daily 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, administered as a single dose or as 100 mg twice per day. Some patients may benefit from a total daily dose of 400 mg.

Special populations

Elderly

No dosage adjustment is necessary. However for elderly patients with a lower than average body weight (50 kg), it is advisable to initiate therapy at the lowest recommended dose.

Hepatic impairment

No dosage adjustment is necessary in patients with mild hepatic impairment. Introduce CELECOXIB ASCENDIS at the lowest recommended dose in patients with moderate hepatic impairment. There is no clinical experience in patients with severe hepatic impairment (see section 4.3).

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 section 4.3).

Paediatric population

CELECOXIB ASCENDIS is not indicated for use in children under 18 years old.

Method of administration

CELECOXIB ASCENDIS may be taken with or without food.

For oral use.

4.3 Contraindications

- Hypersensitivity to celecoxib or to any of the excipients (see section 6.1)
- Known hypersensitivity to sulfonamides.
- Severe impairment of hepatic function (serum albumin < 25 g/L or Child-Pugh score ≥ 10).
- Severe impairment of renal function (creatinine clearance < 30 ml/min).
- Asthma, urticaria or allergic-type reactions precipitated by aspirin or non-steroidal anti-inflammatory medicines, including other cycloxygenase-2 (COX-2) specific inhibitors.
- Established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease.
- Peri-operative analgesia in the setting of coronary artery bypass surgery (CABG).
- Inflammatory bowel disease.
- Active peptic ulceration or gastrointestinal (GI) bleeding.
- In pregnancy and in women of childbearing potential unless using an effective method of contraception (see section 4.6)

- Breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

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

Gastrointestinal (GI) effects

Upper and lower gastrointestinal complications [perforations, ulcers or bleedings (PUBs)] can occur in patients treated with CELECOXIB ASCENDIS, resulting in fatal outcome. 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 acetylsalicylic acid (aspirin) or glucocorticoids concomitantly, patients using alcohol, or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.

There is further increase in the risk of gastrointestinal adverse effects for CELECOXIB ASCENDIS (gastrointestinal ulceration or other gastrointestinal complications) when CELECOXIB ASCENDIS is taken concomitantly with acetylsalicylic acid (even at low doses).

Concomitant NSAID use

The concomitant use of CELECOXIB ASCENDIS and a non-aspirin NSAID should be avoided.

Cardiovascular effects

Increased numbers of serious cardiovascular (CV) events, mainly myocardial infarction, has been documented in long-term usage.

As the cardiovascular risks of CELECOXIB ASCENDIS 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, and 4.8).

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

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thromboembolic diseases because of their lack of antiplatelet effects. Therefore, antiplatelet therapies should not be discontinued.

Fluid retention and oedema

As with other medicines known to inhibit prostaglandin synthesis, fluid retention and oedema have been observed in patients taking CELECOXIB ASCENDIS. Therefore, CELECOXIB ASCENDIS should be used with caution in patients with a 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.

Hypertension

As with all NSAIDS, CELECOXIB ASCENDIS 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 CELECOXIB ASCENDIS 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 CELECOXIB ASCENDIS, may cause renal toxicity. Patients at greatest risk for renal toxicity are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, ACE-inhibitors, angiotensin II receptor antagonists, and the elderly (see section 4.5). Such patients should be carefully monitored while receiving treatment with CELECOXIB ASCENDIS.

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 ASCENDIS. (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 CELECOXIB ASCENDIS therapy should be considered.

CYP2D6 inhibition

CELECOXIB ASCENDIS inhibits CYP2D6. Although it is not a strong inhibitor of this enzyme, a dose reduction 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 (see section 5.2).

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 less frequently in association with the use of CELECOXIB ASCENDIS (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment.

Serious hypersensitivity reactions (including anaphylaxis, angioedema and drug rash with eosinophilia and systemic symptoms (DRESS), or hypersensitivity syndrome), may occur in patients receiving CELECOXIB ASCENDIS (see section 4.8). Patients with a history of sulfonamide allergy or any medicine allergy may be at greater risk of serious skin reactions or hypersensitivity reactions (see section 4.3). CELECOXIB ASCENDIS should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

General

CELECOXIB ASCENDIS may mask fever and other signs of inflammation.

Use with oral anticoagulants

In patients on concurrent therapy with warfarin, serious bleeding events, some of them fatal, have been reported.

Increased prothrombin time (INR) with concurrent therapy has been reported. Therefore, this should be closely monitored in patients receiving

warfarin/coumarin-type oral anticoagulants, particularly when therapy with CELECOXIB ASCENDIS is initiated or CELECOXIB ASCENDIS 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 CELECOXIB ASCENDIS with warfarin or other oral anticoagulants, including novel anticoagulants (e.g. apixaban, dabigatran, and rivaroxaban).

Excipients

CELECOXIB 100 ASCENDIS and CELECOXIB 200 ASCENDIS capsules contain lactose monohydrate (27,07 mg and 54,14 mg, respectively). Patients with rare hereditary problem of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take CELECOXIB ASCENDIS.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

Anticoagulants

Anticoagulant activity should be monitored particularly in the first few days after initiating or changing the dose of CELECOXIB ASCENDIS 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 CELECOXIB ASCENDIS is initiated or the dose of CELECOXIB ASCENDIS is changed (see section 4.4). Bleeding events in association with increases in prothrombin time have been reported, predominantly in the elderly, in patients receiving CELECOXIB ASCENDIS concurrently with warfarin, some of them fatal.

Anti-hypertensives

NSAIDs may reduce the effect of anti-hypertensive medicines including ACE-inhibitors, angiotensin II receptor antagonists, diuretics and beta-blockers. 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, angiotensin II receptor antagonists, and/or diuretics are combined with NSAIDs, including CELECOXIB ASCENDIS (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.

Ciclosporin and tacrolimus

Co-administration of NSAIDs and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin or tacrolimus, respectively. Renal function should be monitored when CELECOXIB ASCENDIS and any of these medicines are combined.

Aspirin

CELECOXIB ASCENDIS can be used with low-dose aspirin but is not a substitute for aspirin for CV prophylaxis. An increased risk of gastrointestinal ulceration or other gastrointestinal complications compared to use of CELECOXIB ASCENDIS alone is shown for concomitant administration of low-dose aspirin.

Pharmacokinetic interactions

Effects of CELECOXIB ASCENDIS 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 CELECOXIB ASCENDIS is used concomitantly. Examples of medicines which are metabolised by CYP2D6 are antidepressants (tricyclics and SSRIs), neuroleptics, anti-dysrhythmic medicines, etc. The dose of individually dose titrated CYP2D6 substrates may need to be reduced when treatment with CELECOXIB ASCENDIS is initiated or increased if treatment with CELECOXIB ASCENDIS is terminated.

Concomitant administration of CELECOXIB ASCENDIS can increase the plasma concentrations of dextromethorphan and metoprolol (CYP2D6 substrates). These increases are due to CELECOXIB ASCENDIS inhibition of the CYP2D6 substrate metabolism.

Methotrexate

Adequate monitoring for methotrexate-related toxicity should be considered when combining these two medicines.

Lithium

Patients on lithium treatment should be closely monitored when CELECOXIB ASCENDIS is introduced or withdrawn.

Effects of other medicines on CELECOXIB ASCENDIS

CYP2C9 poor metabolisers

In individuals who are CYP2C9 poor metabolisers and demonstrate increased systemic exposure to CELECOXIB ASCENDIS, concomitant treatment with CYP2C9 inhibitors such as fluconazole could result in further increases in CELECOXIB ASCENDIS exposure. Such combinations should be avoided in known CYP2C9 poor metabolisers (see sections 4.2 and 5.2).

CYP2C9 inhibitors and inducers

CELECOXIB ASCENDIS is predominantly metabolised by CYP2C9 and it should be used at half the recommended dose in patients receiving fluconazole. Concomitant use of inducers of CYP2C9 such as rifampicin, carbamazepine and barbiturates may reduce plasma concentrations of CELECOXIB ASCENDIS.

4.6 Fertility, pregnancy and lactation

Pregnancy

CELECOXIB ASCENDIS, as with other medicines inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus and should be avoided during pregnancy (see section 4.3).

During the second or third trimester of pregnancy, NSAIDs including CELECOXIB ASCENDIS may cause fetal renal dysfunction which may result in reduction of amniotic fluid volume or oligohydramnios in severe cases. Such effects may occur shortly after treatment initiation and are usually reversible.

CELECOXIB ASCENDIS is contraindicated in pregnancy and in women who can become pregnant (see sections 4.3 and 4.4).

If a woman becomes pregnant during treatment, CELECOXIB ASCENDIS should be discontinued.

Breastfeeding

Limited data indicate that CELECOXIB ASCENDIS is excreted in breast milk and therefore CELECOXIB ASCENDIS should not be used during breastfeeding (see section 4.3).

Fertility

Based on the mechanism of action, the use of NSAIDs, including CELECOXIB ASCENDIS, 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

CELECOXIB ASCENDIS may be associated with dizziness, vertigo or somnolence (see section 4.8). Therefore, patients must be cautious when driving or using machines and should be advised not to drive or operate machinery if they experience these symptoms.

4.8 Undesirable effects

Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequent	Sinusitis, upper respiratory tract infection, pharyngitis, urinary tract infection
Blood and lymphatic system disorders	Less frequent	Anaemia, leukopenia, thrombocytopenia, pancytopenia
Immune system disorders	Frequent	Hypersensitivity
	Less frequent	Anaphylactic shock, anaphylactic reaction, angioedema
Metabolism and nutrition disorders	Less frequent	Hyperkalaemia
Psychiatric disorders	Frequent	Insomnia
	Less frequent	Anxiety, depression, fatigue,

MedDRA system organ class	**Frequency**	**Adverse reactions**
		confusional state, hallucinations
Nervous system disorders	Frequent	Dizziness, hypertonia, headache
	Less frequent	Cerebral infarction, paraesthesia, somnolence, ataxia, dysgeusia, haemorrhage intracranial, (including fatal intracranial haemorrhage), meningitis aseptic, epilepsy (including aggravated epilepsy), ageusia, anosmia
Eye disorders	Less frequent	Vision blurred, conjunctivitis, eye haemorrhage, retinal artery occlusion, retinal vein occlusion
Ear and labyrinth disorders	Less frequent	Tinnitus, hypoacusis
Cardiac disorders	Frequent	Myocardial infarction
	Less frequent	Cardiac failure, palpitations, tachycardia, dysrhythmia
Vascular disorders	Frequent	Hypertension (including aggravated hypertension)
	Less frequent	Pulmonary embolism, flushing, vasculitis
Respiratory, thoracic and mediastinal disorders	Frequent	Pharyngitis, sinusitis, upper respiratory tract infection, rhinitis, cough, dyspnoea

MedDRA system organ class	**Frequency**	**Adverse reactions**
	Less frequent	Bronchospasm, pneumonitis
Gastrointestinal disorders	Frequent	Nausea, abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting, dysphagia
	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, perforation, oesophagitis, melaena, pancreatitis, colitis
Hepato-biliary disorders	Less frequent	Hepatic function abnormal, hepatic enzyme increased (including increased SGOT and SGPT), hepatitis, hepatic failure (sometimes fatal or requiring liver transplant), hepatitis fulminant (some with fatal outcome), hepatic necrosis, cholestasis, hepatitis cholestatic, jaundice
Skin and subcutaneous	Frequent	Rash, pruritus (includes pruritus

MedDRA system organ class	**Frequency**	**Adverse reactions**
tissue disorders		generalised)
	Less frequent	Urticaria, ecchymosis, angioedema, alopecia, photosensitivity, dermatitis, exfoliative, erythema multiform, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), dermatitis, bullous
Musculoskeletal and connective tissue disorders	Frequent	Arthralgia
	Less frequent	Muscle spasms (leg cramps), myositis
Renal and urinary disorders	Frequent Less frequent	Urinary tract infection Blood creatinine increased, blood urea increased, renal failure acute, hyponatraemia, tubulointerstitial nephritis, nephrotic syndrome, glomerulonephritis minimal lesion
Reproductive system and breast disorders	Less frequent	Menstrual disorder

MedDRA system organ class	**Frequency**	**Adverse reactions**
	Frequency unknown	Female fertility decreased
General disorders and administration site conditions	Frequent	Influenza-like illness, oedema peripheral / fluid retention
	Less frequent	Face oedema, chest pain
Injury, poisoning and procedural complications	Fequent	Injury (accidental injury)

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

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 twice daily have been administered without any significant adverse effects. In the event of suspected overdose, appropriate supportive medical care should be provided. Dialysis is unlikely to be an efficient method of medicine removal.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

3.1 Antirheumatics (anti-inflammatory agents)

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, coxibs. ATC code: M01AH01.

Celecoxib is a selective cyclooxygenase 2 inhibitor. Cyclooxygenase 2 (COX-2) is induced in response to inflammatory stimuli. This leads to the synthesis and accumulation of inflammatory prostanoids, in particular prostaglandin E2, causing inflammation, oedema and pain. Celecoxib acts as an anti-inflammatory, analgesic and antipyretic medicine by blocking the production of inflammatory prostanoids via COX-2 inhibition.

In-vivo and *ex-vivo* studies show that celecoxib has a very low affinity for the constitutively expressed cyclooxygenase 1 enzyme (COX-1).

5.2 Pharmacokinetic properties

Absorption

Celecoxib is well absorbed reaching peak plasma concentrations after approximately 2 to 3 hours. Celecoxib exhibits linear and dose proportional pharmacokinetics over the therapeutic dose range. Plasma protein binding, which is concentration independent, is about 97 % at therapeutic plasma concentrations and the medicine is not preferentially bound to erythrocytes in the blood. Dosing with food (high fat meal) delays absorption of celecoxib by about 1 hour resulting in a T_{max} of about 4 hours and increases bioavailability by about 20 %.

Distribution

Plasma protein binding is about 97 % at therapeutic plasma concentrations and the medicine is not preferentially bound to erythrocytes.

Biotransformation

Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites, inactive as COX-1 or COX-2 inhibitors, have been identified in human plasma i.e., a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate.

Cytochrome P450 2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity. Patients who are known, or suspected to be CYP2C9 poor metabolisers based on previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution.

Elimination

Elimination of celecoxib is mostly by hepatic metabolism with less than 1 % of the dose excreted unchanged in urine. After multiple dosing, elimination half-life is 8 to 12 hours and the rate of clearance about 500 ml/min. With multiple dosing steady state plasma concentrations are reached before day 5. The intersubject variability 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 the medicine crosses the blood/brain barrier.

Pharmacokinetics in special patient groups

Elderly/gender

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 being higher in lower weight individuals and consequently higher in the elderly population who are generally of lower mean weight than the younger population. Therefore, elderly females tend to have slightly higher drug plasma

concentrations than elderly males.

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 drug as the main route of metabolism is via the liver.

Renal impairment

There is little experience of celecoxib in renal impairment. The pharmacokinetics of celecoxib has not been studied in patients with renal impairment but is unlikely to be markedly changed in these patients. Thus, caution is advised when treating patients with renal impairment. Severe renal impairment is contraindicated.

Paediatric population

Celecoxib studies have only been performed in adults. Celecoxib is not indicated for use in children under 18 years of age.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Lactose monohydrate

Croscarmellose sodium

Sodium lauryl sulphate

Povidone

Magnesium stearate

Hard gelatin capsule shells

Gelatin

Purified water

Titanium dioxide (CI 77891)

Sodium lauryl sulphate

Printing ink

Shellac (E904)

Dehydrated alcohol (E1510)

Isopropyl alcohol

Butyl alcohol

Propylene glycol (E1520)

Strong ammonia solution (E527)

Indigo carmine (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the outer unit carton until required for use.

6.5 Nature and contents of container.

CELECOXIB ASCENDIS capsules are packed in:

- Aluminium foil and triplex PVC/PE/PVDC clear blisters strips of 10 capsules. Blister strips are stored in an outer unit carton in pack sizes of 10's, 20's, 30's, 60's and 100's.
- 100 capsules packed in a white round HDPE container with a white HDPE cap along with a silica gel bag and sealed with an aluminium tagger. Each container is packed in an outer unit carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ascendis Pharma (Pty) Ltd.

31 Georgian Crescent East

Bryanston

2191

8 REGISTRATION NUMBER(S)

CELECOXIB 100 ASCENDIS: 53/3.1/0015

CELECOXIB 200 ASCENDIS: 53/3.1/0016

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 August 2022

10 DATE OF REVISION OF THE TEXT