SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

DICLOFENAC 25 BIOTECH tablets

DICLOFENAC 100 SR BIOTECH tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DICLOFENAC 25 BIOTECH Tablets: One enteric-coated tablet contains 25 mg diclofenac sodium.

Sugar free.

DICLOFENAC 100 SR BIOTECH Tablets: One tablet contains 100 mg diclofenac sodium.

Sugar free.

For the full list if excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets

DICLOFENAC 25 BIOTECH: round, mustard yellow, biconvex, coated tablets, engraved '25' on one side.

DICLOFENAC 100 SR BIOTECH: round, pink, biconvex tablet, bevel edged, plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DICLOFENAC BIOTECH (diclofenac sodium) is indicated for the symptomatic treatment of:

- Rheumatoid arthritis and osteoarthrosis. It is also used to treat ankylosing spondylitis and spondyarthritis.

- Post-operative and post-traumatic pain associated with inflammation and swelling.
- Pain associated with dental surgery.
- Treatment of the symptoms of primary dysmenorrhoea.

4.2 Posology and method of administration

Posology

The maximum recommended daily dose for DICLOFENAC BIOTECH in any dosage form is 150 mg.

DICLOFENAC BIOTECH should be taken with food and the tablets should be swallowed whole.

Use the lowest effective dose for the shortest possible duration of treatment.

DICLOFENAC 25 BIOTECH Tablets (enteric-coated)

The usual initial daily dose is 100 to 150 mg: in mild cases, DICLOFENAC BIOTECH treatment should be initiated with 75 mg to 100 mg per day. In general, the daily dose should be divided into two or three fractional doses. For the treatment of primary dysmenorrhoea, the dosage should be adapted to meet individual requirements. The daily dosage should be in the range of 50 to 150 mg.

Treatment should begin at the onset of symptoms and continue for a few days.

DICLOFENAC 100 SR BIOTECH Tablets

One tablet to be taken daily. If the symptoms most commonly occur at night or in the morning, the DICLOFENAC BIOTECH should be taken at night.

Paediatric population

DICLOFENAC BIOTECH is not recommended for use in children.

Method of administration

DICLOFENAC BIOTECH tablets are administered orally.

4.3 Contraindications

DICLOFENAC BIOTECH (diclofenac sodium) is absolutely contraindicated in:

- Patients with active or recent history of peptic ulcer.
- Patients with known or suspected hypersensitivity to diclofenac, other non-steroidal anti-inflammatory agents, or any of the excipients in DICLOFENAC BIOTECH listed in section 6.1.
- Asthmatic patients in whom aspirin and other prostaglandin synthetase inhibitors have induced attacks of asthma, acute rhinitis or urticarial.
- Pregnancy and lactation.
- Patients with porphyria.
- Heart failure, established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease.
- History of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including DICLOFENAC BIOTECH.
- Active or history of recurrent ulcer/haemorrhage/perforations.

4.4 Special warnings and precautions for use

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with DICLOFENAC BIOTECH therapy. In view of the DICLOFENAC BIOTECH's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

Caution is required in patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) and should only be treated with DICLOFENAC BIOTECH after careful consideration.

Patients should see a medical practitioner immediately if the patients experience the signs and symptoms of a serious arteriothrombotic event (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings.

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs including DICLOFENAC BIOTECH, especially gastrointestinal perforation, ulceration and bleeding (PUBs) which may be fatal.

Elderly patients receiving DICLOFENAC BIOTECH should be closely monitored, and the dosage reduced if necessary. The lowest effective dose should be used in the elderly, frail and low body mass patients.

The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with increasing doses of DICLOFENAC BIOTECH, in patients with a history of ulcers, and the elderly. Medical supervision is also required for patients with pre-existing dyshaemopoiesis or disorders of blood coagulation.

Gastrointestinal bleeding or perforation may present at any time during DICLOFENAC BIOTECH treatment. This can present with or without warning symptoms or a previous history. When gastrointestinal bleeding or ulceration occurs in patients receiving DICLOFENAC BIOTECH, treatment with DICLOFENAC BIOTECH should be stopped.

To reduce the risk of gastrointestinal toxicity in patients with a history of peptic ulcers, haemorrhage, perforation and in the elderly, the lowest effective dose should be used.

Combination therapy with protective medicines (e.g. proton pump inhibitors) should be considered for these patients as well as for patients that requires concomitant use of medicines containing a low dose acetylsalicylic

acid or other medicines that is likely to increase gastrointestinal risk (see section 4.5).

DICLOFENAC BIOTECH should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated (see section 4.8).

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. DICLOFENAC BIOTECH 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 BIO DICLOFENAC INJECTION. 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 BIO DICLOFENAC INJECTION and evaluate the patient immediately.

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8).

Allergic reactions including anaphylaxis can occur, even without prior exposure. DICLOFENAC BIOTECH like

other medicines that inhibit prostaglandin synthase activity can precipitate bronchospasm. Special precaution is recommended in patients with asthma, seasonal allergic rhinitis, swelling of nasal mucosa, chronic obstructive pulmonary disease or chronic infections of the respiratory tract.

The administration of Nonsteroidal anti-inflammatory drugs (NSAID's) around 20 weeks or later in pregnant patients may cause serious kidney problems in an unborn baby. This may lead to low levels of amniotic fluid because around 20 weeks of pregnancy the unborn baby's kidneys produces amniotic fluid. Amniotic fluid provides a protective cushion and helps the lungs, digestive system, and muscles of the unborn baby to develop (see section 4.3).

Medicines that inhibit prostaglandin synthesis, like NSAID's, may adversely affect pregnancy and/or the embryo or foetal's development. The risk is believed to increase with an increased dose and/or duration of therapy.

Regular use of NSAIDs such as DICLOFENAC BIOTECH during 20 to 40 weeks of pregnancy or the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus *in utero,* and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed, and its duration increased.

DICLOFENAC BIOTECH may cause renal dysfunction, which may progress to renal failure with oligohydroamniosis, and in some cases neonatal renal impairment. Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation. Oligohydramnios may be reversible with treatment. Discontinuation and possible prolongation of bleeding time due to the anti-aggregating effect which may occur even at very low doses of DICLOFENAC BIOTECH.

Fluid retention and oedema have been reported with NSAID therapy, including diclofenac, particular caution

should be taken when DICLOFENAC BIOTECH is used in patients with hepatic or renal insufficiency. Monitoring of renal function is recommended as a precautionary measure when using DICLOFENAC BIOTECH in such cases.

Elevations of one or more of the liver enzymes may occur with DICLOFENAC BIOTECH treatment. Should these abnormal liver functions tests persist or if clinical signs of liver disease develop, DICLOFENAC BIOTECH should be discontinued. Hepatitis may occur.

Serious interactions have been reported with the concomitant use of DICLOFENAC BIOTECH and methotrexate.

Due to the fact that prostaglandins are important where renal blood flow is concerned, careful monitoring is required for the following patients:

- Patients with impaired hepatic, cardiac or renal function.
- Elderly patients being treated with diuretics.
- Patients with extracellular volume depletion.
- Patients with cirrhosis

Patients receiving long term DICLOFENAC BIOTECH therapy should undergo periodic blood counts.
DICLOFENAC BIOTECH may reversibly inhibit platelet aggregation (see section 4.5). Patients with haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.

Patients with collagen disease are at increased risk of developing aseptic meningitis.

DICLOFENAC BIOTECH therapy should be discontinued in patients who experience blurred vision or changes in colour vision.

4.5 Interaction with other medicines and other forms of interaction

NSAIDs: use of two or more NSAIDs concomitantly could result in an increase in side effects.

Anti-hypertensive medicines and diuretics: Concomitant use of DICLOFENAC BIOTECH, with diuretics or antihypertensive medicines (e.g. beta-blockers, angiotensin converting enzyme) may cause a decrease in their antihypertensive effect because of its inhibition of vasodilatory prostaglandin synthesis.

DICLOFENAC BIOTECH may raise plasma concentrations of digoxin or lithium when used concomitantly.

Medicines known to cause hyperkalaemia: Concomitant treatment of DICLOFENAC BIOTECH with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may increase serum potassium levels.

Corticosteroids: increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs).

Bioavailability of DICLOFENAC BIOTECH is reduced by acetylsalicylic acid when the two medicines are administered concomitantly (see section 4.4 for more information).

Anti-coagulants: DICLOFENAC BIOTECH may enhance the effects of anti-coagulants such as warfarin. The patient must be closely monitored due to the increased risk of haemorrhage.

Use of DICLOFENAC BIOTECH in diabetic patients requires close monitoring of blood sugar and possible

alterations in the dosage of hypoglycaemic medicines.

The nephrotoxicity of ciclosporin may be increased when used together with DICLOFENAC BIOTECH due to the effect on renal prostaglandins.

Methotrexate: DICLOFENAC BIOTECH can inhibit the tubular renal clearance and hereby may increased levels of methotrexate.

Tacrolimus: May increase the risk of nephrotoxicity.

Quinolone antimicrobials: Interactions between quinolones and diclofenac may cause convulsions. This may occur in patients without or with history of epilepsy or convulsions.

Phenytoin: Concomitant treatment of diclofenac with phenytoin may increase exposure of phenytoin. For this reason it is recommended to monitor phenytoin plasma concentrations.

Colestipol and cholestyramine: The absorption of diclofenac can be delayed or decreased by these agents. It is recommended to administer diclofenac at least 4 to 6 hours after or one hour before the administration of colestipol or cholestyramine.

Cardiac glycosides: Concomitant use of cardiac NSAID's, like diclofenac, with glycosides may exacerbate cardiac failure, increase plasma glycoside levels and reduce GFR in patients.

Mifepristone: NSAID's like diclofenac, should not be used for 8 to 12 days after administration of mifepristone,

NSAID's can reduce mifepristone's effect.

Potent CYP2C9 inhibitors: Caution is recommended when CYP2C9 is co-administered with DICLOFENAC BIOTECH, this concomitant use could result in an inhibition of diclofenac metabolism that will significant increase in peak plasma concentration and exposure to diclofenac.

Anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

If DICLOFENAC BIOTECH is used by a woman attempting to conceive, the dose should be kept as low and duration of treatment as short as possible.

Pregnancy

DICLOFENAC BIOTECH is contraindicated during pregnancy (see section 4.3).

During the third trimester of pregnancy, all 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;

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Breastfeeding

DICLOFENAC BIOTECH is contraindicated during breastfeeding, due to its ability to pass into the breast milk in small amounts.

Fertility

NSAID's, like DICLOFENAC BIOTECH, may impair female fertility and is not recommended in patients attempting to conceive (see section 4.4).

4.7 Effects on the ability to drive and use machines

Patients who experience central nervous system reactions should refrain from driving and operating hazardous machinery.

4.8 Undesirable effects

Gastrointestinal System	
Frequent	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia, abdominal cramps and discomfort, eructation and local irritation.
Less frequent	Gastritis, gastrointestinal haemorrhage, peptic ulcer with or without perforation, haematemesis, diarrhoea haemorrhagic, melaena, Gastric and duodenal ulcerations with or without bleeding or perforation (sometimes fatal particularly in the elderly). Colitis (including non-specific haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, Aphthous stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, oesophageal lesions, diaphragm-like intestinal strictures, pancreatitis, gastritis.
Unknown	Ischaemic colitis.

Blood and lymphatic system disorders	
Less frequent	Anaemia secondary to gastrointestinal bleeding, thrombocytopenia, leucopoenia, aplastic anaemia, agranulocytosis, haemolytic anaemia, neutropenia, eosinophilia.
Immune system disorders	
Less frequent	Hypersensitivity reactions (e.g.: bronchospasm). anaphylactic and anaphylactoid reactions (including hypotension and shock). Angioneurotic oedema (including face oedema).
Respiratory System	
Less frequent	Asthma (including dyspnoea) in patients sensitive to Acetylsalicylic Acid, pneumonitis.
Psychiatric disorders	
Less frequent	Disorientation, depression, insomnia, nightmares, irritability, psychotic reactions.
Nervous system disorders	
Frequent	Headache, dizziness.
Less frequent	Somnolence, tiredness, drowsiness, vertigo, paraesthesia, memory disturbance, convulsion, anxiety, tremor, aseptic meningitis, impaired concentration, disturbances of sensation, taste alteration disorders, cerebrovascular accident.
Unknown	Confusion, hallucinations, disturbances of sensation, malaise.

Eye disorders	
Less frequent	Disturbances of vision (blurred vision, diplopia), impaired vision, changes in colour perception, toxic amblyopia.
Unknown	Optic neuritis.
Ear and labyrinth disorders	
Frequent	Vertigo.
Less frequent	Tinnitus, impaired hearing.
Cardiac disorders	
Less frequent	Myocardial infarction, cardiac failure, palpitations, chest pain.
Unknown	Kounis syndrome.
Vascular disorders	
Less frequent	Hypertension, sweating, hypotension, vasculitis.
Hepato-biliary disorders	
Frequent	Transaminases increased.
Less Frequent	Liver function disorders including hepatitis with or without jaundice, hepatotoxicity, liver disorder. Fulminant hepatitis, hepatic necrosis, hepatic failure. Elevation of serum aminotransferase enzymes (SGOT, SGPT).
Skin and subcutaneous tissue disorders	
Frequent	Rash.

Less frequent	Urticaria, skin eruption, eczema, erythema, erythema multiforme, bullous reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura including allergic purpura, pruritus.
Frequency unknown	Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) (see section 4.4).
Renal and urinary disorders	
Less frequent	Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis, cystitis.
Reproductive system and breast disorders	
Less frequent	Impotence.
General disorders and administration site conditions	
Less frequent	Oedema, peripheral oedema.

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

See section 4.8.

Treatment is symptomatic and supportive.

There is no specific antidote for DICLOFENAC BIOTECH.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 3.1 Antirheumatics (Anti-inflammatory agents).

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic Products, Non-Steroids.

ATC code: M01AB05

Diclofenac sodium is a non-steroidal agent with anti-inflammatory, analgesic, antirheumatic and antipyretic properties.

5.2 Pharmacokinetic properties

Peak plasma concentrations of diclofenac 25 mg are reached within 1-4 hours and the agent is subject to first p<ISS metabolism. Excretion of the metabolites is mainly via the urine. Diclofenac is 99,7 % protein bound and has a mean terminal elimination half-life of 1-2 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

DICLOFENAC 25 BIOTECH Tablets:

Core:

Colloidal silicon dioxide

Dextrates

Magnesium stearate

Methylcellulose

Stearic acid

Film-Coating:

D&C yellow #10 Lake 15 – 16 % (CI 47005)

Hydroxypropyl methylcellulose (2910)

Polyethylene glycol 3350 (Carbowax)

Sunset yellow lake 40 % (CI 15985)

Titanium dioxide (CI 77891)

Yellow ferric oxide (CI 77492)

DICLOFENAC 100 SR BIOTECH Tablets:

Core:

Dextrates

Hydroxyethyl cellulose (250 HHX)

Magnesium stearate

Microcrystalline cellulose (PH 102)

Film-coating:

Instacoat Universal Pink (A05R00870).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

DICLOFENAC 25 BIOTECH Tablets: 2 years.

DICLOFENAC 100 SR BIOTECH Tablets: 3 years.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light and moisture.

6.5 Nature and contents of the container

DICLOFENAC 25 BIOTECH tablets are packaged in white, plastic bottles of 100 and 500.

DICLOFENAC 100 SR BIOTECH tablets are packaged in white Alu/PVC blister packs of 10 blister per strip, and 3 blister strips per outer carton (pack sizes of 30).

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd.

Ground Floor, Block K West, Central Park

400 16th Road, Randjespark

Midrand

1685

8. REGISTRATION NUMBERS

DICLOFENAC 25 BIOTECH: 30/3.1/0166

DICLOFENAC 100 SR BIOTECH: 30/3.1/0160

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTORISATION

Date of registration:

DICLOFENAC 25 BIOTECH 15 April 1997

DICLOFENAC 100 SR BIOTECH 100: 21 July 1997

10. DATE OF THE REVISION OF THE TEXT

June 2021

SAHPRA approved – 16 November 2021