PACKAGE INSERT

SCHEDULING STATUS:

S2 Status: **10 tablets or less.**

Emergency treatment of acute gout attacks, treatment of post traumatic conditions such as, pain, swelling and inflammation, for a maximum period of 5 days.

S3 Status: **More than 10 tablets.**

Inflammatory and degenerative forms of rheumatism, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and spondylarthritis, painful musculoskeletal conditions, non articular rheumatism, acute gout attacks, and mild to moderately painful post-operative and post-traumatic inflammation and swelling, pain following dental surgery, symptomatic treatment of primary dysmenorrhoea.

PROPRIETARY NAME (AND DOSAGE FORM):

DIFEN SR (TABLET)

COMPOSITION:

Each tablet contains:

Diclofenac Sodium 100mg

PHARMACOLOGICAL CLASSIFICATION:

A 3.1 ANTIRHEUMATICS (ANTI-INFLAMMATORY AGENTS)

PHARMACOLOGICAL ACTION:

Difen SR is a non-steroidal anti-inflammatory medicine (NSAID) with antirheumatic, analgesic and antipyretic properties. It inhibits the activity of the enzyme cyclo-oxygenase, resulting in decreased formation of precursors of prostaglandins and thromboxanes from arachidonic acid.

Difen SR is a slow release preparation designed to release diclofenac over a period of time. It is rapidly absorbed after oral administration. Peak plasma concentrations are reached 2-9 hours after

absorption. Although orally-administered diclofenac is almost completely absorbed and is subject to first-pass metabolism so that only 50 to 60% of the medicine reaches the systemic circulation in the unchanged form. Diclofenac penetrates synovial fluid, readily crosses the placenta and is excreted in breast milk. It is highly protein bound, 99,7%. The terminal plasma half-life is about 1 to 2 hours. It is metabolised to 4-hydroxydiclofenac, 5-hydroxydiclofenac, 3-hydroxydiclofenac and 4,5-dihydroxydiclofenac. It is excreted in the form of glucuronide and sulphate conjugates, mainly in the urine but also in the bile.

INDICATIONS:

Inflammatory and degenerative forms of rheumatism, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and spondylarthritis, painful musculoskeletal conditions, non articular rheumatism, acute gout attacks, and mild to moderately painful post-operative and post-traumatic inflammation and swelling, pain following dental surgery.

Symptomatic treatment of primary dysmenorrhoea.

CONTRA-INDICATIONS:

DIFEN SR should not be used in patients with active gastric or intestinal ulcer or gastrointestinal bleeding and in patients with hypersensitivity to diclofenac sodium. DIFEN SR is contraindicated in asthmatic patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetyl salicylic acid or by other medicines with prostaglandin synthase inhibiting activity.

DIFEN SR should not be used in patients with porphyria, bone marrow depression, pregnancy or children under the age of 2 years.

WARNINGS:

Strict accuracy of diagnosis and careful medical observation is necessary and imperative in patients with symptoms indicative of gastro-intestinal disease or a history of gastro-intestinal ulceration, ulcerative colitis, Crohns disease, in patients suffering from impaired hepatic function and pre-existing dyshaemopoesis or disorders of blood coagulation.

DIFEN SR should be administered with caution in patients with hepatic or renal failure.

Serious interactions have been reported after the concomitant use of methotrexate and DIFEN SR.

Regular use of DIFEN SR during the third trimester of pregnancy may result in premature closure of the foetal ductus arteriosus in utero and possibly in persistent pulmonary hypertension of the new born. The onset of labour may be delayed and its duration increased.

INTERACTIONS:

Difen SR may increase plasma concentrations of lithium, digoxin and methotrexate. Concomitant use of Difen SR and other NSAIDs may increase the frequency of side effects. Concomitant use of Difen SR and glucocorticoids may aggravate the gastro-intestinal side effects. Difen SR may increase cyclosporin nephrotoxicity as a result of their effect on renal prostaglandins. There is an increased risk of convulsions if quinolone antibiotics are given while Difen SR is being taken, and caution is advised when considering their use. Increased serum potassium levels may result when Difen SR is given concomitantly with potassium-sparing diuretics. Serum potassium levels should therefore be monitored. Care is required when giving anticoagulants with Difen SR as it may reversibly inhibit platelet aggregation and increase risk haemorrhagea. Non-steroidal anti-inflammatory drugs (NSAIDs) may increase the hypoglycemic effect of antidiabetic agents; dosage adjustments of the diabetic agent may be necessary; glipizide and glyburide may not be affected as much as the other oral antidiabetic agents, however, caution with concurrent use is recommended. Difen SR has also been reported to decrease the effects of antidiabetic agents, leading to hyperglycemia.

PREGNANCY AND LACTATION:

Contra-indicated in pregnancy and lactation.

Regular use of NSAIDs during the third trimester of pregnancy may result in premature closure of the foetal ductus arteriosus in utero and possibly in persistent pulmonary hypertension of the new born. The onset of labour may be delayed and its duration increased.

Following doses of 100mg/day, no active substance could be found in breast milk (Limit of detection

10ng/ml).

DOSAGE AND DIRECTIONS FOR USE:

Adults -Oral, one 100 mg tablet a day. Tablets should be swallowed whole preferably with food.

Elderly -Care should be used when treating patients who are frail or have a low body weight as they will in general be more susceptible to adverse reactions. The lowest effective dose should be used in these patients. The standard adult dose may be used for other elderly patients.

Children -Not suitable for use in children.

Note: The tablets should not be fragmented nor chewed.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

The following **common side effects** have been reported:

Gastro Intestinal Disorders

Nausea, headache, diarrhoea, epigastric pain, dyspepsia, anorexia, flatulence and abdominal cramps.

Nervous System Disorders

Vertigo, nervousness and dizziness.

The following **less common side effects** have been reported:

Gastro Intestinal Disorders

Bloody diarrhoea, gastric or intestinal ulcer with or without bleeding or perforation, haematemesis and melaena.

Nervous System Disorders

Tiredness, disturbance of sensation (parasthesia) and memory, disorientation, insomnia, irritability, convulsions, tremor, disturbances of vision (blurred and diplopia), hearing and taste.

Psychiatric Disorders

Depression, anxiety, nightmare and psychotic reactions.

Skin and Subcutaneous Tissue Disorders

Skin rashes and eruptions.

Hepato- Biliary Disorders

Elevated transaminase levels (SGO1 and SGP1).

The following **rare side effects** have been reported:

Blood and the Lymphatic System Disorders

Leucopenia, haemolytic anaemia, thrombocytopenia, aplastic anaemia and agranulocytosis and nose bleeds.

Skin and Subcutaneous Tissue Disorders

Urticaria, bulbous eruptions, eczema, erythema multiforme, Steven Johnson's Syndrome, Lyell's Syndrome (acute toxic epidermolysis), erythroderma (exfoliative dermatitis), loss of hair, photosensitivity reactions, purpura including allergic purpura.

Hypersensitivity reactions (anaphylactic/ anaphylactoid) systemic reactions.

Cardiac Disorders

Hypotension and bronchospasm. Many of the following cardiovascular effects may occur secondary to NSAID induced renal function impairment: angina pectoris, irregular heartbeat, congestive heart failure and increased blood pressure.

In view of the inherent potential of NSAIDs to cause fluid retention, heart failure may be precipitated in some compromised patients.

Renal and Urinary Disorders

Oedema, acute renal insufficiency, urinary abnormalities (eg. Haematuria, proteinuria), nephrotic syndrome, papillary necrosis and interstitial nephritis.

Hepato- biliary Disorders

Elevation of serum aminotransferase enzymes (ALT, AST) and liver function disorders.

Special Precautions

Dosage may have to be reduced in the elderly. In particular, it is recommended that the lowest effective dosage be used in frail elderly patients or those who have low body mass.

Owing to the importance of prostaglandins for maintaining renal blood flow, patients suffering from impairment of hepatic, cardiac or renal function, as well as the elderly, patients being treated with diuretics, those with extracellular volume depletion from any cause e.g. The peri- or post-operative phase of major surgical operations should be carefully monitored.

KNOWN SYMPTOMS OF OVER DOSAGE AND PARTICULARS OF ITS TREATMENT:

See side effects and special precautions.

Gastrointestinal symptoms (e.g. abdominal pain, nausea, vomiting); central nervous system effects (eg. lethargy, drowsiness) and renal effects have been reported. More serious effects such as gastrointestinal haemorrhage, acute renal failure, convulsions and coma have also been reported.

Treatment for overdosage: gastric lavage and treatment with activated charcoal should be used as soon as possible after overdosage in order to prevent absorption of the medicine. Further treatment is supportive and symptomatic.

IDENTIFICATION:

Round, pink film-coated, bevel-edged with shallow convex faces.

PRESENTATION:

Push through PVC/Aluminium blister strips of 10 tablets in a pack of 100 in a unit carton.

Opaque plastic containers containing 30, 60, 100, 500 or 1000 tablets.

STORAGE INSTRUCTIONS:

Store below 25ºC. Protect from moisture.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER (OR REFERENCE NUMBER):

37/3.1/0641

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Gulf Drug Company (Pty) Ltd

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Mount Edgecombe, 4300

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