1.5.5 Clinical Professional Information and Patient Information Leaflet

amendments/updates

1.5.5.1 Annotated Professional Information for medicines for human use (clean)

**SCHEDULING STATUS:** **S3**

**PROPRIETARY NAMES (and dosage forms):**

**MYLAN DICLOFENAC 25 mg** (Tablets)

**MYLAN DICLOFENAC 50 mg** (Tablets)

**MYLAN DICLOFENAC INJECTION** (Injection)

**COMPOSITION:**

Enteric-coated tablets containing 25 mg or 50 mg diclofenac sodium.

Each 25 mg tablet contains 85 mg lactose monohydrate (sugar).

Each 50 mg tablet contains 86 mg lactose monohydrate (sugar).

Each 3 ml ampoule contains 75 mg diclofenac sodium with 4 % v/v benzyl alcohol as a preservative.

**PHARMACOLOGICAL CLASSIFICATION:**

A 3.1 Anti-rheumatics (anti-inflammatory) agents.

**PHARMACOLOGICAL ACTION:**

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

Diclofenac sodium is eliminated principally by metabolism and subsequent urinary and biliary excretion of glucuronide and sulphate conjugates of the metabolites.

The principal metabolite in man is the 4-hydroxy derivative of diclofenac sodium.

The amount excreted in urine accounts for 20 to 30 % of the dose and that in bile for 10 to 20 %. The mean terminal elimination half-life is 1,2 to 1,8 hours.

**Tablets:** A single 50 mg dose of enteric-coated tablets results in maximum plasma concentrations of about 1 500 ng/ml at 1,5 to 2 hours after ingestion.

**INDICATIONS:**

**Tablets:**

Rheumatoid arthritis, osteo-arthritis and ankylosing spondylitis.

Treatment of post-traumatic pain and inflammation.

Symptomatic treatment of primary dysmenorrhoea.

**Injection:**

For use as initial therapy for inflammatory and degenerative rheumatic diseases. Painful conditions due to inflammation of non-rheumatic origin and acute attacks of gout.

**CONTRA-INDICATIONS:**

Patients with a history of active gastro-intestinal bleeding or perforation (PUBs) related to previous NSAIDs. Active, or history of recurrent ulcer/haemorrhage/perforations. Severe hepatic or renal impairment and heart failure. Contra-indicated in aspirin-sensitive patients, and in patients hypersensitive to any of the ingredients of these products.

**WARNINGS:**

Serious interactions have been reported after the use of a high dose methotrexate with diclofenac.

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

**MYLAN DICLOFENAC** may mask the signs and symptoms of infection due to its pharmacodynamic properties. 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 **MYLAN DICLOFENAC.**

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

The risk of gastrointestinal bleeding or perforation (PUBs) is higher with increasing doses of **MYLAN DICLOFENAC**, in patients with a history of ulcers, and the elderly.

When gastrointestinal bleeding or ulceration occurs in patients receiving **MYLAN DICLOFENAC** treatment with **MYLAN DICLOFENAC** should be stopped.

**MYLAN DICLOFENAC** 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.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson's syndrome and toxic epidermal necrolysis have been reported. **MYLAN DICLOFENAC** should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

**INTERACTIONS:**

Do not take **MYLAN DICLOFENAC** concomitantly with methotrexate as serious interactions have been reported after the use of high dose methotrexate with diclofenac.

Use of two or more NSAIDs (non-steroidal anti-inflammatory) concomitantly could result in an increase in side effects.

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (PUBs).

Anti-coagulants: **MYLAN DICLOFENAC** may enhance the effects of anti-coagulants such as warfarin.

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

**PREGNANCY AND LACTATION:**

Safety during pregnancy has not been established.

**DOSAGE AND DIRECTIONS FOR USE:**

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

**MYLAN DICLOFENAC 25 mg and 50 mg Tablets:**

In adults the dosage is 25 to 50 mg three times daily depending on the severity of the condition. The maintenance dose should be adjusted to the minimum that will provide continuous control. The tablets should be swallowed whole, with or after a meal. The dosage in children is 2 mg per kilogram body mass daily.

**MYLAN DICLOFENAC Injection:**

For adults: 75 mg deep intragluteal injection into the outer upper quadrant once daily, or two times daily, in severe or hospitalised cases. Each injection must be given at a different site. Not to be given by intravenous injection. The directions for intramuscular injection must be followed in order to avoid damage to a nerve or other tissue at the injection site. After inserting the needle, the plunger should be pulled back to avoid inadvertent intra-arterial injection. Each injection should be separated by an interval of a few hours. Parenteral administration should not be given for more than two days; if necessary the treatment can be continued by oral therapy.

**SIDE-EFFECTS AND SPECIAL PRECAUTIONS:**

**Side-effects:**

Haematological:

- *Less frequent:* Leucopenia, thrombocytopenia, aplastic anaemia, haemolytic anaemia, agranulocytosis.

Cardiovascular system:

- *Less frequent:* Palpitations, chest pain, hypertension; congestive heart failure, oedema and cardiac failure.

Nervous system disorders:

- *Frequent:* Headache, dizziness, vertigo, nervousness.
- *Less frequent:* Tiredness, disturbances of sensation (including paraesthesia), memory disturbance, disorientation, insomnia, irritability, convulsions, depression, anxiety, nightmares, tremor, psychotic reactions, aseptic meningitis.

Gastrointestinal:

- *Frequent:* Epigastric pain, nausea, vomiting, diarrhoea, constipation, abdominal cramps, dyspepsia, flatulence, eructation, anorexia, local irritation.
- *Less frequent:* Gastrointestinal bleeding, haematemesis, melaena, bloody diarrhoea, peptic ulcer with or without bleeding or perforation, lower gut disorders such as non-specific haemorrhagic colitis, exacerbation of ulcerative colitis or Crohn's proctocolitis, gastritis, glossitis, aphthous stomatitis, oesophageal lesions, diaphragm-like intestinal strictures, constipation, pancreatitis, alteration of taste.

Kidney/Genitourinary:

- *Less frequent:* Acute renal failure, urinary abnormalities such as haematuria, proteinuria, interstitial nephritis, nephritic syndrome, papillary necrosis.

Liver:

- *Frequent:* Elevated transaminase levels (ALT, AST).
- *Less frequent:* Hepatitis with or without jaundice, fulminant hepatitis.

Ocular:

- *Less frequent:* Disturbances of vision (diplopia, blurred vision).

Skin:

- *Frequent:* Rash and skin reactions.

- *Less frequent:* Urticaria, bullous eruptions, eczema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (acute toxic epidermolysis), erythroderma (exfoliative dermatitis), loss of hair, photosensitivity reaction, purpura, including allergic purpura.

Other:

- *Less frequent:* Impaired hearing, tinnitus. Hypersensitivity reactions (such as bronchospasm, anaphylactic systemic reactions including hypotension), vasculitis and pneumonitis may occur without prior exposure to **MYLAN DICLOFENAC**. Discontinue treatment immediately.
- Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) [see Warnings and Precautions].

**Special Precautions:**

**MYLAN DICLOFENAC** should be given with care to patients with cardiovascular disease, bleeding disorders, in those who are receiving coumarin anti-coagulants, and in patients with impaired hepatic or renal function.

**MYLAN DICLOFENAC** may mask the signs and symptoms of infection due to its pharmacodynamic properties.

Acute allergic reactions have been reported. Because of the possibility of cross-sensitivity due to structural relationships, which exist among non-steroidal anti-inflammatory medicines, acute allergic reactions may be more likely to occur in patients who have exhibited allergic reactions to these compounds. Allergic reactions, which include angio-oedema, bronchospasm, urticaria and anaphylactic reactions, have occurred. In view of

the product's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

Injections of **MYLAN DICLOFENAC** may cause local pain and irritation; abscesses and local necrosis have been reported. Plasma concentrations are significantly decreased by the concomitant administration of therapeutic doses of aspirin. When given together with preparations containing lithium or digoxin, diclofenac sodium may raise their plasma concentrations. Concomitant administration of glucocorticoids or other non-steroidal anti-inflammatory agents may aggravate gastro-intestinal side-effects.

Concurrent administration with two or more non-steroidal anti-inflammatory agents may promote the occurrence of side-effects.

Should be used with caution in patients with asthma or bronchoconstriction.

Use carefully in elderly patients. Decreased platelet aggregation with increased bleeding time may occur. May increase the half-life of probenecid. Use with care together with other protein-bound medicines, e.g. tolbutamide, coumarin and hydantoin.

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**

See "SIDE EFFECTS AND SPECIAL PRECAUTIONS". Treatment is symptomatic and supportive.

**IDENTIFICATION:**

**Tablets:**

25 mg tablets: A Yellowish-mustard, enteric coated, normal biconvex tablets.

50 mg tablets: A Light brown, enteric coated, normal biconvex tablets.

**Injection:**

Clear, colourless, to slightly amber solution in amber ampoules.

**PRESENTATION:**

**Tablets:**

25 mg tablets:

Blister packs of 9, 10, 15, 42, 84, 100 or 500 tablets or Securitainers of 100 or 500 tablets.

50 mg tablets:

Blister packs of 9, 10, 15, 18 or 21 tablets or Securitainers with 500 tablets.

**Injections:**

Amber glass ampoules in packs of 5 or 50.

**STORAGE INSTRUCTIONS:**

Store below 25 °C.

Protect tablets from moisture.

Do not remove tablets from the outer carton until required for use.

Protect ampoules from heat and light.

Do not refrigerate ampoules.

KEEP OUT OF REACH OF CHILDREN.

**REGISTRATION NUMBERS:**

25 mg tablets: Y/3.1/148

50 mg tablets: Y/3.1/149

Injection: Z/3.1/265

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

Mylan (Pty) Ltd

4 Brewery Street

Isando

1600

Republic of South Africa

**DATE OF PUBLICATION OF THIS PACKAGE INSERT:**

Tablets: 31 August 1990

Injection: 29 November 1991