1.5.5.1 Annotated Professional Information for medicines for human use – clean

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

MYLAN DICLOFENAC INJECTION (Injection)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each 3 ml ampoule contains 75 mg diclofenac sodium.

Excipients(s) with known effect:

Preservative: Benzyl Alcohol 4 % *m/v*

For full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Injection:

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Posology

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

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.

Method of administration

Intramuscular injection.

Contraindications

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

- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- **MYLAN DICLOFENAC** is also contraindicated in asthmatic patients in whom attacks of asthma, urticarial or acute rhinitis are precipitated by acetylsalicylic acid or by other nonsteroidal ant-inflammatory drugs (NSAIDs).
- **MYLAN DICLOFENAC** should not be used in patients with porphyria.
- Pregnancy *(see section 4.6*)
- Children *(see section 4.2).*

4.4 Special warnings and precautions for use

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.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (*see section 4.2*)
The concomitant use of **MYLAN DICLOFENAC** with systemic NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the absence of any

evidence demonstrating synergistic benefits and the potential for additive undesirable effects (*see section 4.5*).

Caution is indicated in the elderly on basic medical grounds. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight *(see section 4.2*).

As with other nonsteroidal anti-inflammatory drugs including diclofenac as contained in **MYLAN DICLOFENAC,** allergic reactions, including anaphylactic/anaphylactoid reactions can also occur without earlier exposure to the medicine (*see section 4.8*). Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to **MYLAN DICLOFENAC.**

Serious interactions have been reported after the use of a high dose methotrexate with diclofenac (*see section 4.5*).

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

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.

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.

Injections of **MYLAN DICLOFENAC** may cause local pain and irritation; abscesses and local necrosis have been reported.

Use with care together with other protein-bound medicines, e.g. tolbutamide, coumarin and hydantoin (*see section 4.5)*.

Renal effects:

- Caution is required in patients with a history of hypertension and/or heart failure and renal function, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function and those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery as fluid retention and oedema have been reported in association with MYLAN DICLOFENAC. (see section 4.3) Monitoring of renal function is recommended as a precautionary measure when using MYLAN DICLOFENAC in such cases. Discontinuation therapy is usually followed by recovery to the pre-treatment state.

Gastrointestinal effects:

- When gastrointestinal bleeding or ulceration occurs in patients receiving **MYLAN DICLOFENAC** treatment with **MYLAN DICLOFENAC** should be stopped. They generally have more serious consequences in the elderly.
- **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. The risk of gastrointestinal bleeding (GI bleeding), ulceration or perforation is higher with increasing NSAID doses including diclofenac as contained in **MYLAN DICLOFENAC**, and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation.
- **Elderly:**

Use carefully in elderly patients. The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation (PUBs) which may be fatal.

- To reduce the risk of gastrointestinal (GI) toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low dose acetylsalicylic acid (ASA/aspirin or medicinal products likely to increase gastrointestinal risk *(see section 4.5).*
- Patients with a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding).
- Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors (SSRIs) or anti-platelet agents such as acetylsalicylic acid (*see section 4.5*).
- NSAIDs, including diclofenac as contained in **MYLAN DICLOFENAC**, may be associated with increased risk of gastrointestinal anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac after gastro-intestinal surgery.

Skin effects:

- 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.

Hepatic effects:

- Close medical surveillance is required when prescribing **MYLAN DICLOFENAC** to patients with impairment of hepatic function as their condition may be exacerbated.
- As with other NSAIDs, including diclofenac as contained in **MYLAN DICLOFENAC**, values of one or more liver enzymes may increase. During prolonged treatment with **MYLAN DICLOFENAC**, regular monitoring of hepatic function is indicated as a precautionary measure.
- If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), **MYLAN DICLOFENAC** should be discontinued.
- Hepatitis may occur with **MYLAN DICLOFENAC** without prodromal symptoms.
- Caution is called for when using **MYLAN DICLOFENAC** in patients with hepatic porphyria, since it may trigger an attack.

SLE and mixed connective tissue disease:

- 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)*.

Cardiovascular and cerebrovascular effects:

- In view of the product's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.
- Patients with congestive heart failure (NYHA-I) or patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with **MYLAN DICLOFENAC** after careful consideration.
- As the cardiovascular risks of diclofenac as contained in **MYLAN DICLOFENAC** may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.
- Appropriate monitoring and advice are required for patients with a history of hypertension and congestive heart failure (NYHA-I) as fluid retention and oedema have been reported in association with NSAID therapy including diclofenac as contained in **MYLAN DICLOFENAC**.
- Patients should remain alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. Patients should be instructed to see a physician immediately in case of such an event.

Haematological effects:

- Decreased platelet aggregation with increased bleeding time may occur.
- During prolonged treatment with diclofenac as contained in **MYLAN DICLOFENAC**, as with other NSAIDs, monitoring of the blood count is recommended.

- **MYLAN DICLOFENAC** may reversibly inhibit platelet aggregation *(see anticoagulants in section 4.5*). Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.

Pre-existing asthma:

- Should be used with caution in patients with asthma or bronchoconstriction.
- In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so called intolerance to analgesics / analgesics asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria.
- Like other medicines that inhibit prostaglandin synthetase activity, **MYLAN DICLOFENAC** and other NSAIDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of bronchial asthma.

DICLOFENAC contains benzyl alcohol

This medicine benzyl alcohol that may cause allergic reactions *(see section 2).*

Interaction with other medicines and other forms of interaction

Methotrexate:

Do not take **MYLAN DICLOFENAC** concomitantly with methotrexate as serious interactions have been reported after the use of high dose methotrexate with diclofenac. Caution is recommended when **MYLAN DICLOFENAC** is administered less than 24 hours before or after treatment with methotrexate.

Lithium:

If used concomitantly, **MYLAN DICLOFENAC** may raise plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

Digoxin:

If used concomitantly, **MYLAN DICLOFENAC** may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

Diuretics and antihypertensive agents:

Concomitant use of **MYLAN DICLOFENAC** with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity. Concomitant treatment with potassium-sparing drugs may be associated with increased serum potassium levels, which should therefore be monitored frequently *(see section 4.4).*

Other NSAIDs and corticosteroids:

Concomitant administration of **MYLAN DICLOFENAC** and corticosteroids may aggrevate the frequency of gastrointestinal undesirable effects e.g. increased risk of gastrointestinal ulceration or bleeding (PUBs) *(see section 4.4)*.

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

Anticoagulants and anti-platelet agents:

Plasma concentrations are significantly decreased by the concomitant administration of therapeutic doses of aspirin.

MYLAN DICLOFENAC may enhance the effects of anti-coagulants such as warfarin. The bioavailability of **MYLAN DICLOFENAC** is reduced by acetylsalicylic acid, and that of acetylsalicylic acid by **MYLAN DICLOFENAC**, when the two agents are administered together. Caution is recommended since concomitant administration could increase the risk of bleeding (*see section 4.4).* There are reports of an increased risk of haemorrhage in patients receiving **MYLAN DICLOFENAC** and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Selective serotonin reuptake inhibitors (SSRIs):

Concomitant administration of systemic NSAIDs and SSRIs may increase the risk of gastrointestinal bleeding *(see section 4.4).*

Antidiabetics:

There have been isolated reports of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with **MYLAN DICLOFENAC**.

For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Ciclosporin:

MYLAN DICLOFENAC may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.

Quinolone antibacterials:

There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.

Medicines known to cause hyperkalemia:

Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored *(see section 4.4).*

Tacrolimus:

Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. This might be mediated through renal antiprostagladin effects of both NSAID and calcineurin inhibitor.

Phenytoin:

When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

Colestipol and cholestyramine:

These agents can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/ cholestyramine.

Cardiac glycosides:

Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Mifepristone:

NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Potent CYP2C9 inhibitors:

Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

May increase the half-life of probenecid.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

No information available.

Pregnancy

Safety during pregnancy has not been established.

MYLAN DICLOFENAC should not be used during the first two trimesters of pregnancy. Use during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia and/or premature closure of the ductus arteriosus *(see section 4.3).*

Breastfeeding

MYLAN DICLOFENAC passes into the breast milk in small amounts. Therefore, **MYLAN DICLOFENAC** should not be administered during breastfeeding in order to avoid undesirable effects in the infant.

Fertility

The use of **MYLAN DICLOFENAC** may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of **MYLAN DICLOFENAC** should be considered.

4.7 Effects on ability to drive and use machines

MYLAN DICLOFENAC may cause visual disturbances, dizziness, vertigo, somnolence, central nervous system disturbances, drowsiness or fatigue and have no or negligible effect on mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

4.8 Undesirable effects

Tabulated list of adverse reactions

Infection and Infestations	
Unknown	Injection site necrosis.

Blood and lymphatic system disorders	
Less frequent	Thrombocytopenia, leucopoenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.
Immune system disorders	
Less frequent	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock). Angioneurotic oedema (including face oedema).
Psychiatric disorders	
Less frequent	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders	
Frequent Less frequent Unknown	Headache, dizziness, nervousness. Somnolence, tiredness. Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident, irritability, depression, nightmares, psychotic reactions. Confusion, hallucinations, disturbances of sensation, malaise.
Eye disorders	
Less frequent Unknown	Visual disturbance, vision blurred, diplopia. Optic neuritis.
Ear and labyrinth disorders	
Frequent Less frequent	Vertigo. Tinnitus, hearing impaired.
Cardiac disorders	
Less frequent	Myocardial infarction, cardiac failure, palpitations, chest pain, congestive heart failure.
Not known	Kounis syndrome.

Vascular disorders	
Less frequent	Hypertension, hypotension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Less frequent	Asthma (including dyspnoea). Pneumonitis.
Gastrointestinal disorders	
Frequent	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia, abdominal cramps, eructation, local irritation.
Less frequent	Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer with or without bleeding or perforation (sometimes fatal particularly in the elderly). Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis, alteration of taste.
Unknown	Ischaemic colitis.
Hepatobiliary disorders	
Frequent	Transaminases increased.
Less frequent	Hepatitis, jaundice, liver disorder. Fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders	
Frequent	Rash.
Less frequent	Urticaria. Bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus.

Renal and urinary disorders	
Less frequent	Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.
Reproductive system and breast disorders	
Less frequent	Impotence.
General disorders and administration site conditions	
Frequent Less frequent	Injection site reaction, injection site pain, injection site induration. Oedema.

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 professionals are asked to report any suspected adverse reactions to SAHPRA via the “Report Drug Reaction Process”, found online under SAHPRA’s safety publications: https://www.sahpra.org.za/

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity. See section 4.8.

Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Pharmacotherapeutic group: Non-steroidal Anti-inflammatory and antirheumatic products, non-steroids, acetic acid derivatives and related substances (NSAID) (ATC code: M01A B05).

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

5.2 Pharmacokinetic 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol

Water for injection

6.2 Incompatibilities

The ampoules should not be mixed with other injection solutions.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 25 °C.

Protect ampoules from heat and light.

Do not refrigerate ampoules.

Store in the original package/container.

6.5 Nature and contents of container

Injections:

Amber glass ampoules in packs of 5 or 50.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Mylan (Pty) Ltd

4 Brewery Street

Isando

1600

Republic of South Africa

8 REGISTRATION NUMBER(S)

Injection: Z/3.1/265

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Injection: 29 November 1991

10 DATE OF REVISION OF TEXT

TBA