Professional Information (PI)

for Medicines for Human Use

DICLOFENAC INJECTION UNIMED (Injection)

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

DICLOFENAC INJECTION UNIMED (75 mg/3 ml)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 3 ml ampoule contains:

Diclofenac sodium 75 mg

Benzyl alcohol 4 % *m/v* as preservative

Sodium metabisulphite 0,1 % *m/v* as an antioxidant

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Injection

Ampoules 75 mg / 3 ml: Clear, colourless to pale yellow solution free from fibers and particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, ankylosing spondylitis, osteoarthrosis and spondylarthritis.
- Painful musculoskeletal conditions.
- Non-articular rheumatism.
- Acute attacks of gout.
- Painful post-operative and post-traumatic inflammation and swelling, pain following dental surgery.
- Symptomatic treatment of primary dysmenorrhoea.

DICLOFENAC INJECTION UNIMED is suitable as initial therapy for inflammatory and degenerative rheumatic diseases, as well as for the treatment of painful conditions due to inflammation of non-rheumatic origin.

4.2 Posology and method of administration

Posology

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

Adults:

For adults the dosage is generally one **DICLOFENAC INJECTION UNIMED** ampoule daily.
DICLOFENAC INJECTION UNIMED should not be mixed with other injection solutions. By way of exception, in severe cases, two injections separated by an interval of a few hours can be given per day (one into each buttock).
DICLOFENAC INJECTION UNIMED should not be given for more than two days.

Paediatric population

DICLOFENAC INJECTION UNIMED is not suitable for use in children.

Method of administration

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.

Not intended for the intravenous route of administration.

Only for deep intragluteal injection into the upper outer quadrant.

4.3 Contraindications

- Peptic ulcer.
- Hypersensitivity to diclofenac sodium, sodium metabisulphite, or to any excipients in **DICLOFENAC INJECTION UNIMED** (see section 6.1).
- **DICLOFENAC INJECTION UNIMED** is also contraindicated in asthmatic patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or by other NSAIDs.
- History of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including **DICLOFENAC INJECTION UNIMED**.
- Active or history of recurrent ulcer/haemorrhage/perforations.
- Heart failure, established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease.
- **DICLOFENAC INJECTION UNIMED** should not be used in patients with porphyria.
- Hepatic or renal failure (see section 4.4).
- Patients sensitive to any other non-steroidal anti-inflammatory medicine.
- Pregnant women from around 20 weeks of gestation and later in pregnancy due to the risks of oligohydramnios/ foetal renal dysfunction and premature closure of the foetal ductus arteriosus (see section 4.4 and 4.6).

- Lactation (see section 4.6).
- Children (see section 4.2).

4.4 Special warnings and precautions for use

General

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2).

Strict accuracy of diagnosis and close medical surveillance are imperative in patients with symptoms indicative of gastrointestinal disease, a case history suggestive of gastrointestinal ulceration, ulcerative colitis, Crohn's disease, pre-existing dyshaemopoiesis or disorders of blood coagulation.

DICLOFENAC INJECTION UNIMED should be administered with caution in patients with hepatic or renal failure. Serious interactions have been reported after the concomitant use of high dose methotrexate and diclofenac, as in **DICLOFENAC INJECTION UNIMED** (see section 4.5).

Allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to **DICLOFENAC INJECTION UNIMED** (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 diclofenac, as in **DICLOFENAC INJECTION UNIMED.**

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

DICLOFENAC INJECTION UNIMED should be discontinued in patients who experience blurred or diminished vision, or changes in colour vision.

Cardiovascular and cerebrovascular effects

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 INJECTION UNIMED** therapy.

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 after careful consideration.

As the cardiovascular risks of diclofenac, as in **DICLOFENAC INJECTION UNIMED**, 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).

Data consistently point towards increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, as in **DICLOFENAC INJECTION UNIMED** particularly at high dose (150 mg daily).

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 medical practitioner immediately in case of such an event.

In view of **DICLOFENAC INJECTION UNIMED's** inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

Elderly

There are generally more serious consequences in the elderly. **DICLOFENAC INJECTION UNIMED** should be used with care as the elderly has an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforations (PUBs), which may be fatal.

The risk of GI (gastrointestinal) bleeding is higher with increasing **DICLOFENAC INJECTION UNIMED** doses and in patients with a history of ulcers, particularly if complicated with haemorrhage or perforation and in the elderly (see section 4.3).

Caution is indicated in the elderly on basic medical grounds. The elderly must receive close monitoring. Dosage may have to be reduced in the elderly. In particular, it is recommended that the lowest effective dose be used in frail, elderly patients or those with a low body mass.

Gastrointestinal effects

Gastrointestinal bleeding (haematemesis, melaena), ulceration or perforation, which can be fatal, have been reported with diclofenac, as in **DICLOFENAC INJECTION UNIMED** and may

occur at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events.

To reduce the risk of 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.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding). Caution is recommended in patients receiving concomitant medicines which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, anti-platelet medicines or selective serotonin-reuptake inhibitors (see section 4.5).

Close medical surveillance is imperative and particular caution should be exercised when prescribing **DICLOFENAC INJECTION UNIMED** in patients with symptoms indicative of gastrointestinal disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see section 4.8).

Close medical surveillance and caution should also be exercised in patients with gastrointestinal disease and a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as their condition may be exacerbated (see section 4.8).

In the instances where peptic ulceration or gastrointestinal bleeding occur in patients under treatment with **DICLOFENAC INJECTION UNIMED** the medicine should be withdrawn.

Combination therapy with protective medicines (e.g. proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant use of medicines containing low-dose acetylsalicylic acid (aspirin) or other medicines likely to increase gastrointestinal risk (see section 4.5).

NSAIDs, including diclofenac, as in **DICLOFENAC INJECTION UNIMED**, may be associated with increased risk of GI anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac, as in **DICLOFENAC INJECTION UNIMED**, after GI surgery.

Serious skin reactions

Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) have been reported. **DICLOFENAC INJECTION UNIMED** should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity (see section 4.8).

Patients appear to be at highest risk of 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.

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as **DICLOFENAC INJECTION UNIMED**. 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. Eosinophilia 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 **DICLOFENAC INJECTION UNIMED** and evaluate the patient immediately.

Pregnancy:

It is recommended that **DICLOFENAC INJECTION UNIMED** is avoided in pregnant women at 20 weeks or later in pregnancy (see section 4.3 and 4.6).

Avoid prescribing NSAIDs, such as diclofenac as in **DICLOFENAC INJECTION UNIMED**, at 30 weeks and later in pregnancy because of the additional risk of premature closure of the foetal ductus arteriosus (see section 4.6).

The use of NSAIDs, such as diclofenac, as in **DICLOFENAC INJECTION UNIMED**, around 20 weeks gestation or later in pregnancy may cause foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation. In some post marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between 20 weeks and 30 weeks gestation, limit **DICLOFENAC INJECTION UNIMED** use to the lowest effective dose and shortest duration

possible.

Healthcare professionals should consider ultrasound monitoring of amniotic fluid if **DICLOFENAC INJECTION UNIMED** treatment extends beyond 48 hours. Discontinue **DICLOFENAC INJECTION UNIMED** if oligohydramnios occurs and follow up according to clinical practice.

Pre-existing asthma

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 to **DICLOFENAC INJECTION UNIMED** 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 medicines, e.g. with skin reactions, pruritus or urticaria see section 4.3)

Hepatic impairment

Close medical surveillance is required when prescribing **DICLOFENAC INJECTION UNIMED** to patients with impaired hepatic function, as their condition may be exacerbated.

Elevations of one or more liver enzymes may occur with **DICLOFENAC INJECTION UNIMED**. During prolonged treatment with **DICLOFENAC INJECTION UNIMED**, blood counts and monitoring of hepatic function is indicated.

If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with

liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash, etc.) **DICLOFENAC INJECTION UNIMED** should be discontinued. Hepatitis may occur without prodromal symptoms. Caution is called for when using **DICLOFENAC INJECTION UNIMED** in patients with hepatic porphyria, since it may trigger an attack.

Renal effects

As fluid retention and oedema have been reported in association with **DICLOFENAC INJECTION UNIMED** therapy, particular caution is called for in patients with impaired cardiac, or renal function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicines that can significantly impact renal function, and in those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery (see section 4.3). Monitoring of renal function is recommended as a precautionary measure when using **DICLOFENAC INJECTION UNIMED** in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

Renal Tubular Acidosis

Severe hypokalaemia and renal tubular acidosis have been reported due to prolonged use of NSAIDs at higher than recommended doses. Presenting signs and symptoms included generalised weakness. NSAID induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

Haematological effects

During prolonged treatment with **DICLOFENAC INJECTION UNIMED**, monitoring of the blood count is recommended.

Diclofenac, as in **DICLOFENAC INJECTION UNIMED** may reversibly inhibit platelet

aggregation, decreased platelet aggregation with increased bleeding time may occur (see section 4.5). Patients with defects of haemostasis bleeding diathesis or haematological abnormalities should be carefully monitored.

Anaemia may occur as a result of water retention or effects on erythropoiesis. Consequently, it is advisable to monitor the levels of haemoglobin and haematocrit if symptoms of anaemia are detected. Hyperpotassemia may occur in diabetic patients or those who are also taking potassium-sparing medicines (see section 4.5).

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).

Female fertility

The use of **DICLOFENAC INJECTION UNIMED** may impair female fertility and is not recommended in women attempting to conceive. In women who may have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of **DICLOFENAC INJECTION UNIMED** should be considered (see section 4.6).

Injection site reactions

Injection site reactions have been reported after the administration of **DICLOFENAC INJECTION UNIMED**, including injection site necrosis and embolia cutis medicamentosa, also known as Nicolau Syndrome (particularly after inadvertent subcutaneous administration). **DICLOFENAC INJECTION UNIMED** must be carried out following strict rules of asepsis and antisepsis (see section 4.2).

The instructions for intramuscular injection should be strictly followed in order to avoid

undesirable effects at the injection site, which may result in muscle weakness, muscle paralysis, hypoaesthesia and injection site necrosis (see section 4.2 and 4.8).

Excipients

DICLOFENAC INJECTION UNIMED contains 600 mg propylene glycol per 3 ml ampoule which is equivalent to 200 mg/ml.

DICLOFENAC INJECTION UNIMED contains 120 mg benzyl alcohol per 3 ml ampoule which is equivalent to 40 mg/ml. Benzyl alcohol may cause allergic reactions. Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding or if you have liver or kidney disease. This is because large amounts of benzyl alcohol can build up in your body and may cause side effects (called “metabolic acidosis”).

The presence of sodium metabisulphite can, especially in patients with bronchial asthma, lead to isolated hypersensitivity reactions, which may become manifest as an acute asthma attack, clouding of consciousness, or shock (see section 4.3).

4.5 Interaction with other medicines and other forms of interaction

NSAIDs, corticosteroids and acetylsalicylic acid (aspirin)

Concomitant administration of glucocorticoids or other non-steroidal anti-inflammatory agents, may aggravate gastrointestinal side effects. Concurrent treatment with two or more non-steroidal anti-inflammatory agents may promote the occurrence of side effects.

The bioavailability of **DICLOFENAC INJECTION UNIMED** is reduced by acetylsalicylic acid, and that of acetylsalicylic acid by **DICLOFENAC INJECTION UNIMED**, when the two medicines are administered together.

Lithium

If used concomitantly, **DICLOFENAC INJECTION UNIMED** may raise plasma concentrations of lithium. NSAIDs, such as **DICLOFENAC INJECTION UNIMED** have been reported to increase blood lithium levels via decreased renal excretion of lithium. If this combination is considered necessary, lithium plasma concentrations should be monitored carefully during the initiation, adjustment and withdrawal of diclofenac, as in **DICLOFENAC INJECTION UNIMED** treatment.

Digoxin

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

Diuretics and antihypertensive medicines

Concomitant use of **DICLOFENAC INJECTION UNIMED** with diuretics or antihypertensive medicines (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin-II antagonists and medicines that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. 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.

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 frequently (see section 4.4).

Anticoagulants

There are reports of an increased risk of haemorrhage with the combined use of **DICLOFENAC INJECTION UNIMED** and anticoagulant therapy. Therefore close monitoring of such patients is recommended.

NSAIDs, such as **DICLOFENAC INJECTION UNIMED,** may enhance the effects of anticoagulants such as warfarin and heparin.

Thrombolytics and anti-platelet medicines

Caution is recommended since concomitant administration with NSAIDs, such as **DICLOFENAC INJECTION UNIMED**, could cause increased risk of bleeding via inhibition of platelet function and damage to the gastroduodenal mucosa.

Selective serotonin reuptake inhibitors (SSRIs)

Concomitant administration of systemic NSAIDs, such as **DICLOFENAC INJECTION UNIMED** and SSRIs may increase the risk of gastrointestinal bleeding (see section 4.4).

Antidiabetics

Data have shown that diclofenac, as in **DICLOFENAC INJECTION UNIMED** can be given together with oral antidiabetic medicines without influencing their clinical effect, however, there have been reports of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic medicines during treatment with diclofenac, as in **DICLOFENAC INJECTION UNIMED**. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Methotrexate

Diclofenac, as in **DICLOFENAC INJECTION UNIMED**, can inhibit the tubular renal clearance of methotrexate thereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, as in **DICLOFENAC INJECTION UNIMED**, are administered less than 24 hours before or after treatment with methotrexate, since blood concentrations of methotrexate may rise, and the toxicity of this medicine be increased. Weekly blood count monitoring during the first few weeks of the combination is recommended. Monitoring should be increased in patients with impaired kidney function or in the elderly.

Pemetrexed in patients with normal renal function, CrCl > 80 ml/min

Increased risk of pemetrexed toxicity due to decrease in pemetrexed clearance. Biological monitoring of renal function is recommended.

Calcineurin inhibitors (e.g. Ciclosporin, tacrolimus)

Nephrotoxicity of calcineurin inhibitors may be enhanced by NSAIDs, such as **DICLOFENAC INJECTION UNIMED**, via renal prostaglandin mediated effects. During combined treatment, monitoring of renal function is recommended, especially in the elderly.

Deferasirox

The concomitant administration of NSAIDs, such as **DICLOFENAC INJECTION UNIMED** and deferasirox may increase the risk of gastrointestinal toxicity. Close clinical monitoring should be performed when these medicines are combined.

Quinolone antibacterials

Convulsions may occur due to an interaction between quinolones and NSAIDs, such as

diclofenac, as in **DICLOFENAC INJECTION UNIMED**. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving D**ICLOFENAC INJECTION UNIMED**.

Phenytoin

When using phenytoin concomitantly with diclofenac, as in **DICLOFENAC INJECTION UNIME**D, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

Colestipol and cholestyramine

These medicines can induce a delay or decrease in absorption of diclofenac, as in **DICLOFENAC INJECTION UNIMED**. Therefore, it is recommended to administer **DICLOFENAC INJECTION UNIME**D at least one hour before or 4 to 6 hours after administration of colestipol/ cholestyramine.

Potent CYP2C9 inhibitors

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

Mifepristone

DICLOFENAC INJECTION UNIMED should not be used for 8 to 12 days after mifepristone administration as **DICLOFENAC INJECTION UNIMED** can reduce the effect of mifepristone.

General

Acute allergic reactions have been reported. Because of the possibility of cross sensitivity due to structural relationships that exist among nonsteroidal anti-inflammatory medicines, acute allergic reactions may be more likely to occur in patients who have exhibited allergic reactions to these compounds.

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

DICLOFENAC INJECTION UNIMED may increase the half-life of probenecid.

Use with care together with other protein-bound medicines e.g. tolbutamide, coumarin and hydantoin.

4.6 Fertility, pregnancy and lactation

DICLOFENAC INJECTION UNIMED should not be given to pregnant woman or lactating women (see section 4.3 and 4.4).

Pregnancy

It is recommended that **DICLOFENAC INJECTION UNIMED** is avoided in pregnant women at 20 weeks or later in pregnancy (see section 4.3 and 4.4).

Avoid prescribing NSAIDs, such as diclofenac as in **DICLOFENAC INJECTION UNIMED**, at 30 weeks and later in pregnancy because of the additional risk of premature closure of the foetal ductus arteriosus (see section 4.3 and 4.4).

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the

embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation wis increased from less than 1 %, up to approximately 1,5 %.

The risk is believed to increase with dose and duration of therapy.

In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, diclofenac, as in **DICLOFENAC INJECTION UNIMED**, should not be given unless clearly necessary. If diclofenac, as in **DICLOFENAC INJECTION UNIMED** is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible (see section 4.4).

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, as in **DICLOFENAC INJECTION UNIMED** passes into the breast milk in small amounts. Therefore, **DICLOFENAC INJECTION UNIMED** should not be administered during breast feeding in order to avoid undesirable effects in the infant (see section 4.3).

Fertility

The use of **DICLOFENAC INJECTION UNIMED** 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 **DICLOFENAC INJECTION UNIMED** should be considered (see section 4.4).

4.7 Effects on ability to drive and use machines

Since adverse reactions such as dizziness, vertigo, somnolence, blurred vision and other ocular reactions have been reported in patients receiving **DICLOFENAC INJECTION UNIMED**, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that **DICLOFENAC INJECTION UNIMED** does not adversely affect their ability to do so (see section 4.8).

4.8 Undesirable effects

~~a~~*) Summary of the safety profile*

The most commonly observed adverse events are gastrointestinal in nature or injection site reactions which are generally mild and transitory.

Data suggest that the use of diclofenac injectable solution, such as **DICLOFENAC INJECTION UNIMED**, is associated with injection site reactions, such as pain and haematoma.

After administering diclofenac, as in **DICLOFENAC INJECTION UNIMED** the following have also been reported: nausea, vomiting, diarrhoea and constipation. Abscesses and local

necrosis have also occurred, particularly in elderly diabetics.

The known adverse reactions with **DICLOFENAC INJECTION UNIMED** when used intramuscularly were injection site reactions, often related to an administration procedure, including pain at the injection site, erythema and rash. In some cases, hypersensitivity reactions also with generalised symptoms have been reported after treatment.

b) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Infections and infestations		Injection site abscess.	
Blood and the lymphatic system disorders		Dyshaemopoiesis (leucopoenia, thrombocytopenia, anaemia (including aplastic and haemolytic anaemia, agranulocytosis).	
Immune system disorders		Hypersensitivity reactions (e.g. bronchospasm, anaphylactic/ anaphylactoid systemic reactions including hypotension and shock),	

		angioneurotic oedema (including facial oedema).	
Metabolism and Nutrition Disorders			Hypokalaemia*
Psychiatric disorders		Disorientation insomnia, irritability, depression, nightmare, psychotic disorder.	Agitation.
Nervous system disorders	Headache, dizziness, vertigo	Somnolence, tiredness, disturbances of sensation (including paraesthesia), memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.	Drowsiness, nervousness. confusion, hallucinations, malaise.
Eye disorders		Visual disturbances, blurred vision, diplopia.	Ocular reactions optic neuritis.
Ear and labyrinth disorders		Impaired hearing, tinnitus.	
Cardiac disorders		Palpitations, chest pain, cardiac failure, myocardial infarction.	Oedema.
Vascular disorders		Hypertension, vasculitis.	
Respiratory, thoracic and mediastinal		Asthma (including dyspnoea), pneumonitis, bronchospasm.	

disorders			
<u>Gastrointestinal disorders</u>	Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, epigastric pain, nausea, vomiting, diarrhoea, abdominal cramps, dyspepsia, flatulence, eructation, anorexia, local irritation, constipation, abdominal pain, haematemesis, melaena, ulcerative stomatitis, gastritis.	Gastrointestinal ulcer (with or without bleeding) or perforation, haemorrhagic diarrhoea, colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease, stomatitis, glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis.	Ischaemic colitis.
Hepatobiliary disorders	Elevated transaminase levels (SGOT, SGPT)	Hepatitis, jaundice, fulminant hepatitis**,** liver disorder, increase in hepatic enzymes, hepatic necrosis, hepatic failure.	Abnormalities of liver function tests.
Skin and subcutaneous tissue disorders	Rash and skin reactions.	Urticaria. Bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome,	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).

		Lyell's syndrome (toxic epidermolysis necrolysis), erythroderma (exfoliative dermatitis), loss of hair, photosensitivity reaction, purpura, including allergic purpura, prutitis.	
Musculoskeletal and connective tissue disorders	Limb discomfort		
Renal and urinary disorders		Acute renal failure, urinary abnormalities such as haematuria, proteinuria, interstitial nephritis, nephrotic syndrome, renal papillary necrosis.	Renal function impairment. Renal tubular acidosis*
Reproductive system and breast disorders		Impotence.	
General disorders and administrative site conditions	Injection site reactions, injection site pain, injection site induration.	Injection site necrosis.	Nicolau syndrome.

*Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of higher than recommended doses.

c) Description of selected adverse reactions

Allergic reactions which include angio-oedema, bronchospasm, urticaria and anaphylactic reactions have occurred.

Data consistently point towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, as in **DICLOFENAC INJECTION UNIMED**, particularly at high doses (150 mg daily) (see section 4.3 and 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. 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

Symptoms

There is no typical clinical picture resulting from **DICLOFENAC INJECTION UNIMED** overdosage. Overdosage can cause symptoms such as vomiting, epigastric pain, gastrointestinal haemorrhage, diarrhoea, dizziness, disorientation, excitation, coma, drowsiness, tinnitus, fainting or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible.

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8).

Treatment

There is no specific antidote. Symptomatic and general supportive measures. Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastro-intestinal irritation and respiratory depression. Specific therapies such as forced diuresis, dialysis, or haemoperfusion are probably of no help in eliminating **DICLOFENAC INJECTION UNIMED** because of its high protein-binding rate and extensive metabolism. Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patient's clinical condition.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A 3.1 Antirheumatics (anti-inflammatory agents)

Pharmacotherapeutic group: Non-steroidal anti-inflammatory drugs (NSAIDs):

ATC code: M01AB05

Mechanism of action

DICLOFENAC INJECTION UNIMED is a non-steroidal compound with antirheumatic, anti-inflammatory, analgesic and antipyretic properties. *In vitro* its active substance strongly inhibits prostaglandin-synthetase and also has an inhibitory effect on platelet aggregation. Inhibition of prostaglandin biosynthesis, which has been demonstrated experimentally, is regarded as having an important bearing on its mechanism of action. Prostaglandins play a

major role in the causation of inflammation, pain and fever.

DICLOFENAC INJECTION UNIMED exerts an analgesic effect within 30 minutes in moderately and severely painful states of non-rheumatic origin.

5.2 Pharmacokinetic properties

Distribution

Peak plasma concentrations are attained 10 to 22 minutes after an intramuscular dose of **DICLOFENAC INJECTION UNIMED.**

Protein binding: 99,7 %.

Elimination

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

Approximately 60 % of the dose administered is excreted via the kidneys in the form of metabolites, and less than 1 % in unchanged form. About 30 % of the dose is excreted in metabolised form in the faeces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol

Disodium edetate

5 % *v/v* Hydrochloric acid solution (for pH adjustment)

Propylene glycol

5 % *w/v* Sodium hydroxide solution (for pH adjustment)

Sodium metabisulphite

Water for injection

6.2 Incompatibilities

DICLOFENAC INJECTION UNIMED should not be mixed with other injection solutions.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ºC. Protect from light.

DO NOT FREEZE.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

3 ml colourless and transparent USP type I glass ampoule, packed in pack sizes of 10 x 3 ml or 50 x 3 ml ampoules.

6.6 Special precautions for disposal

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) Ltd

Corner Birch Road and Bluegum Avenue,

Anchorville,

Lenasia,

1827,

South Africa

8. REGISTRATION NUMBER

31/3.1/0334

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

07 May 2001

10. DATE OF REVISION OF THE TEXT

27 July 2023