Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Diclac 25 mg/ml Solution for Injection 3 ml Ampoule

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 3ml ampoule contains 75 mg Diclofenac Sodium (25 mg/ml)
Excipients with known effect:
Each 3 ml ampoule contains 120 mg of benzyl alcohol (40 mg/ml) and 600 mg propylene glycol (200 mg/ ml).
For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection.
Colourless to slightly yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Intramuscular injection:
Treatment of
- exacerbation of inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, osteoarthritis
- renal colic and biliary colic
- acute attacks of gout
- acute trauma and fractures
- post traumatic and post-operative pain, inflammation and swelling.

Intravenous infusion:
- For treatment or prevention of post-operative pain in the hospital setting

4.2 Posology and method of administration

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (See section 4.4 Special warnings and special precautions for use). Diclac ampoules should not be given for more than 2 days, if necessary treatment can be continued with tablets or suppositories.

Route of Administration:

For intravenous infusion or intramuscular use only Intravenous use:
Diclac should not be administered by intravenous bolus injection Immediately before starting an intravenous infusion, diclofenac solution for injection must be diluted. For Instruction on dilution of the product before administration, see section 6.6.
Two alternative dosage regimens of diclofenac solution for injection are recommended.

For the treatment of moderate to severe post-operative pain, 75 mg should be infused continuously over a period of 30 minutes to 2 hours. If necessary, treatment may be repeated after 4-6 hours, but the dose should not exceed 150 mg within any period of 24 hours.
For the prevention of post-operative pain, a loading dose of 25 mg to 50 mg should be infused after surgery over 15 minutes to 1 hour, followed by a continuous infusion of about 5 mg per hour up to a maximum daily dose of 150 mg.

Intramuscular use: Recommended Dosage Schedule:

The following directions for intramuscular injection must be followed in order to avoid damage to a nerve or other tissue at the injection site.

One ampoule once (or in severe cases twice) daily intramuscularly by deep intragluteal injection into the upper outer quadrant. If two injections daily are required, it is advised the alternative buttock be used for the second injection.
Alternatively, one ampoule of 75 mg can be combined with other pharmaceutical forms of diclofenac (e.g. tablets, suppositories) up to a maximum daily dose of 150 mg.

Renal Colic:
One 75 mg ampoule intramuscularly. A further ampoule may be administered after 30 minutes if necessary. The recommended maximum daily dose of Diclac is 150 mg.

Older people (Patients aged 65 or above):
Although the pharmacokinetics of Diclac are not impaired to any clinically relevant extent in elderly patients, non-steroidal anti-inflammatory drugs should be used with particular caution in such patients who generally are more prone to adverse reactions. In particular it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight. Prolonged use of non-steroidal anti-inflammatory drugs in the elderly is not recommended (see Section 4.4).

Congestive Heart Failure (NYHA-I) or significant cardiovascular risk factors
Patients with congestive heart failure (NYHA-I) or significant risk factors for cardiovascular events should be treated with Diclac only after careful consideration and only at doses ≤100 mg daily if treated for more than 4 weeks (see section 4.4 Special warnings and precautions for use).

Renal impairment
Diclofenac is contraindicated in patients with severe renal impairment (see section 4.3).
No specific studies have been carried out in patients with renal impairment, therefore, no specific dose adjustment recommendations can be made.
Caution is advised when administering diclofenac to patients with mild to moderate renal impairment (see section 4.3 and 4.4).

Hepatic impairment
Diclofenac is contraindicated in patients with severe hepatic impairment (see section 4.3).
No specific studies have been carried out in patients with hepatic impairment, therefore, no specific dose adjustment recommendations can be made.
Caution is advised when administering diclofenac to patients with mild to moderate hepatic impairment (see section 4.3 and 4.4).

Children and adolescents (under 18 years):
Diclac solution for injection is not suitable for children and adolescents. Diclac injection are contraindicated in children up to 14 years (see section 4.3)

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- History of gastrointestinal bleeding or perforation related to previous NSAIDs therapy. Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)

- Active gastric or intestinal ulcer, bleeding or perforation

- Third trimester of pregnancy (see section 4.6 Pregnancy and Lactation)

- Hepatic failure

- Chronic Kidney Disease Grade 5 (GFR <15)

- Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contra-indicated in patients in whom the use of acetylsalicyclic acid or other NSAIDs can precipitate asthma, angioedema, urticaria, or acute rhinitis.

- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

- Diclac injections are contraindicated in children up to 14 years.

4.4 Special warnings and precautions for use

General:
As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug. 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.

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2 and GI and cardiovascular risks below).

The concomitant use of Diclac 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.

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.

Like other NSAIDs, diclofenac may mask the signs and symptoms of infection due to its pharmacodynamic properties.

The instructions for intramuscular injection should be strictly followed in order to avoid adverse events at the injection site, which may result in muscle weakness, muscle paralysis, hypoaesthesia embolia cutis medicamentosa (Nicolaou syndrome) and injection site necrosis.

Diclofenac solution for injection must not be given to premature babies or neonates. Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years of age.

Gastrointestinal effects
Gastrointestinal bleeding, ulceration or perforation, which can be fatal, have been reported with all NSAIDs including diclofenac and may occur at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving diclofenac, the medicinal product should be withdrawn.

As with all NSAIDs including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing diclofenac in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, patients with ulcerative colitis or Crohn's disease and in patients suffering from impaired hepatic function, bleeding or perforation (see section 4.8). The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3). The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

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.

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

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

Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated (see section 4.8).

NSAIDs, including diclofenac, may be associated with increased risk of gastro-intestinal anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac after gastro-intestinal surgery.

Hepatic effects
Close medical surveillance is required when prescribing diclofenac to patients with impaired hepatic function, as their condition may be exacerbated.

As with other NSAIDs including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with diclofenac (e.g. in the form of tablets or suppositories), regular monitoring of hepatic function is indicated as a precautionary measure. 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 should be discontinued.

Hepatitis may occur with diclofenac without prodromal symptoms.

Caution is called for when using diclofenac in patients with hepatic porphyria, since it may trigger an attack.

Renal effects
As fluid retention and oedema have been reported in association with NSAID therapy including diclofenac, particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment being treated with diuretics or medicinal products that can significantly impact renal function (e.g. aminoglycosides), 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 in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

Skin Effects
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis and generalised bullous fixed drug eruption have been reported very rarely in association with the use of diclofenac (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. Diclac should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.
Injection site reactions
Injection site reactions have been reported after the administration of diclofenac intramuscularly, including injection site necrosis and embolia cutis medicamentosa, also known as Nicolau syndrome (particularly after inadvertent subcutaneous administration). Appropriate needle selection and injection technique should be followed during intramuscular administration of diclofenac (see sections 4.2 and 6.6).

Cardiovascular and cerebrovascular effects
Appropriate monitoring and advice are required for patients with a history of hypertension and/or congestive heart failure (NYHA-1) as fluid retention and oedema have been reported in association with NSAID therapy.
Clinical trial and epidemiological data suggest that the use of diclofenac, particularly at high dose (150mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).
Patients with congestive heart failure (NYHA-1) and patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration.
As the cardiovascular risks of 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.
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
During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of the blood count is recommended.
Like other NSAIDs, diclofenac may temporarily inhibit platelet aggregation. Patients with defects of haemostasis should be carefully monitored.

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 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.
Special caution is recommended when diclofenac is used parenterally in patients with bronchial asthma because symptoms may be exacerbated.
This medicine contains less than 1 mmol sodium (23 mg) per 3 ml ampoule that is to say essentially sodium free.
This medicine contains 200 mg propylene glycol in each ml, which is equivalent to 600 mg in a 3 ml ampoule.
Each 3 ml ampoule contains 120 mg benzyl alcohol. Benzyl alcohol may cause allergic reactions. High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment, because of the risk of accumulation and toxicity (metabolic acidosis).

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions include those observed with diclofenac solution for injection and/or other pharmaceutical forms of diclofenac.

Observed interactions to be considered

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 inhibitions of diclofenac metabolism.

Lithium: If used concomitantly, diclofenac may raise plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

Digoxin: if used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

Diuretics and antihypertensive agents: Like other NSAIDs, concomitant use of diclofenac, with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis. Therefore, the combination should be administered with caution in 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 increase risk of nephrotoxicity (see section 4.4).

Ciclosporin: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.
Tacrolimus: Possible increased risk of nephrotoxicity when NSAID's are given with tacrolimus. This might be mediated through renal antiprostaglandin effects of both NSAID and calcineurin inhibitor.

Drugs 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).

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

Anticipated interactions to be considered:

Other NSAIDs and corticosteriods: Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal ulceration or bleeding (see section 4.4).

Anticoagulants and anti-platelet agents:
Caution is recommended since concomitant administration could increase the risk of bleeding (see section 4.4). Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4).
There are isolated reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of systemic NSAID including diclofenac and SSRIs may increase the risk of gastrointestinal bleeding (see section 4.4).

Antidiabetics: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic hypoglycaemic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Methotrexate: Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels.

Caution is recommended when NSAIDs including diclofenac are administered less than 24 hours before or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.

Cases of serious toxicity have been reported when methotrexate and NSAIDs including diclofenac are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.

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 NSAID's in patients may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Mifepristone: NSAID's should not be used for 8-12 days after mifepristone administration as NSAID's can reduce the effect of mifepristone.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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 was increased from less than 1%, up to approximately 1.5 %.
The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post- implantation loss and embryo-foetal lethality.

In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. From the 20th week of pregnancy onward, diclofenac use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, diclofenac should not be given unless clearly necessary. If diclofenac 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. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to diclofenac for several days from gestational week 20 onward. Diclofenac should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, (see above).

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.
Consequently, diclofenac is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Lactation

Like other NSAIDs, diclofenac passes into the breast milk, but in small amounts. Therefore, diclofenac should not be administered during breast feeding in order to avoid undesirable effects in the infant.

Fertility

As with other NSAIDs, the use of 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 diclofenac should be considered.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness, vertigo, somnolence or other central nervous system disturbances, including visual disturbances, while taking NSAIDs, should refrain from driving or using machines.

4.8 Undesirable effects

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention:

Common; (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, <1/100); rare (≥ 1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4 Special warnings and special precautions for use).

The following undesirable effects include those reported with diclofenac solution for injection and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

Infections and infestations:
Very rare: Injection site abscess
Blood and lymphatic disorders
Very rare: Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis
Immune system disorders
Rare: Hypersensitivity reactions such as asthma, systemic anaphylactic and anaphylactoid reactions (including hypotension and shock)
Very rare: Angioedema (including face oedema)
Psychiatric disorders
Very rare: Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder
Nervous system disorders
Common: Headache, dizziness Rare: Somnolence
Very rare: Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, dysgeusia, cerebrovascular accident
Eye disorders
Very rare: Visual impairment (blurred vision, diplopia)
Ear and labyrinth disorders

Common: Vertigo
Very rare: Tinnitus, hearing impaired

Cardiac disorders
Uncommon*: Myocardial infarction, cardiac failure, palpitations, chest pain
Not known: Kounis syndrome

Vascular disorders
Very rare: Hypertension, vasculitis

Respiratory, thoracic and mediastinal disorders
Rare: Asthma/bronchospasm (including dyspnoea)
Very rare: Pneumonitis

Gastrointestinal tract disorders
Common: Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, decreased appetite
Rare: Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastric or intestinal ulcer (with or without bleeding or perforation)
Very rare: Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal lesions, diaphragm-like intestinal strictures, pancreatitis

Hepatobiliary disorders
Common: Transaminases increased
Rare: Hepatitis with or without jaundice, liver disorder
Very rare: Fulminant hepatitis, hepatic necrosis, hepatic failure

Skin and subcutaneous tissue disorders
Common: Rash
Rare: Urticaria
Very rare: Dermatitis bullous, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, alopecia, photosensitivity reaction, purpura, Henoch-Schonlein purpura, pruritus
Frequency not known: Fixed drug eruptions, generalised fixed drug eruptions

Renal and urinary disorders
Very rare: Acute renal failure, haematuria, proteinuria, nephritic syndrome, tubulointerstitial nephritis, renal papillary necrosis

General disorders and administration site conditions
Common: Injection site reactions such as local pain and induration
Rare: Oedema, injection site necrosis.
Not Known: Embolia cutis medicamentosa (Nicolau syndrome)

*the frequency reflects data from long-term treatment with a high dose (150mg/day).
Clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke associated with the use of diclofenac, particularly at high dose (150mg daily) and in long term treatment (see section 4.3 and 4.4).
Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie

4.9 Overdose

Symptoms
There is no typical clinical picture resulting from diclofenac overdosage. Overdosage can cause symptoms such as vomiting, gastrointestinal haemorrhage, diarrhoea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible.

Therapeutic measures
Management of acute poisoning with NSAIDs, including diclofenac, consists essentially of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.
Special measures such as forced diuresis, dialysis or haemoperfusion are probably unlikely to be helpful in accelerating the elimination of NSAIDs, including diclofenac, because of their high protein binding rate and extensive metabolism.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
Diclac contains diclofenac sodium, a non-steroidal compound with pronounced antirheumatic, anti-inflammatory, analgesic, and antipyretic properties. Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, is considered fundamental to its mechanism of action. Prostaglandins play a major role in causing inflammation, pain and fever.

Diclofenac sodium *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to those reached in humans.

Pharmacodynamic effects
In rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac elicit a clinical response characterised by marked relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness, and swelling of the joints, as well as by an improvement in function.

Diclofenac has also been found to exert a pronounced analgesic effect in moderate and severe pain of non-rheumatic origin, an effect which sets in within 15 to 30 minutes.

Diclofenac has also been shown to have a beneficial effect in migraine attacks.

In post-traumatic and post-operative inflammatory conditions, diclofenac rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound oedema.

When used concomitantly with opioids for the management of post-operative pain, diclofenac significantly reduces the need for opioids.

Diclofenac ampoules are particularly suitable for initial treatment of inflammatory and degenerative rheumatic diseases and of painful conditions due to inflammation of non-rheumatic origin.

There is limited clinical trial experience of the use of diclofenac in Juvenile Rheumatoid Arthritis (JRA)/Juvenile Idiopathic Arthritis (JIA) paediatric patients.

In a randomized, double-blind, 2-week, parallel group study in children aged 3-15 years with JRA/JIA, the efficacy and safety of daily 2-3 mg/kg BW diclofenac was compared with acetylsalicylic acid (ASS, 50-100 mg/kg BW/d) and placebo – 15 patients in each group. In the global evaluation, 11 of 15 diclofenac patients, 6 of 12 aspirin and 4 of 15 placebo patients showed improvement with the difference being statistically significant ($p < 0.05$). The number of tender joints decreased with diclofenac and ASS but increased with placebo. In a second randomized, double-blind, 6-week, parallel group study in children aged 4-15 years with JRA/JIA, the efficacy of diclofenac (daily dose 2-3 mg/kg BW, n=22) was comparable with that of indomethacin (daily dose 2-3mg/kg BW, n=23).

5.2 Pharmacokinetic properties

Absorption:
After administration of 75 mg diclofenac by intramuscular injection, absorption sets in immediately and mean peak plasma concentrations of about 2.558 ± 0.968 micrograms/ml (2.5 microgram/mL = 8 micromol/L) are reached after about 20 minutes.

When 75 mg diclofenac is administered as an intravenous infusion over 2 hours, mean peak plasma concentrations are about 1.9 micrograms/mL (5.9 micromol/L). Shorter infusions result in higher peak plasma concentrations, while longer infusions give plateau concentrations proportional to the infusion rate after 3 to 4 hours. In contrast, plasma concentrations decline rapidly once peak levels have been reached following intramuscular injection or administration of gastro-resistant tablets or suppositories.

The area under the concentration curve (AUC) after intramuscular administration or intravenous administration is about twice as large as it is following oral or rectal administration, because about half the active substance is metabolised during its first passage through the liver ("first pass" effect) when administered via the oral or rectal routes. The amount absorbed is in linear proportion to the size of the dose.

Pharmacokinetic behaviour does not change on repeated administration. Accumulation does not occur provided the recommended dosage intervals are observed.

Distribution:
The active substance is 99.7% protein bound, mainly to albumin (99.4%).
Diclofenac enters the synovial fluid, where maximum concentrations are measured 2-4 hours after the peak plasma values have been attained. The apparent half-life for elimination from the synovial fluid is 3-6 hours. Two hours after reaching the peak plasma values, concentrations of the active substance are already higher in the synovial fluid than they are in the plasma and remain higher for up to 12 hours.
Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother. The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03 mg/kg/day dose.

Biotransformation/Metabolism:
Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites most of which are converted to glucuronide conjugates. Two phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.

Elimination:
Total systemic clearance of diclofenac in plasma is 263 ± 56 ml /min (mean value ±SD). The terminal half-life in plasma is 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1-3 hours.
About 60% of the administered dose is excreted in the urine as the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

Special Populations:

Elderly:
No relevant age-dependent differences in the drug's absorption, metabolism or excretion have been observed, other than the finding that in five elderly patients, a 15-minute IV infusion resulted in 50% higher plasma concentrations than expected with young healthy subjects.
Patients with renal impairment: In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of <10ml/min, the calculated steady-state plasma levels of the hydroxyl metabolites are about 4 times higher than in normal subjects. However, the metaboli**te**s are ultimately cleared through the bile.
Patients with hepatic disease: In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

5.3 Preclinical safety data

Preclinical data from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, and carcinogenicity studies with diclofenac revealed no specific hazard for humans at the intended therapeutic doses. In standard preclinical animal studies, there was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits.

Diclofenac has no influence on the fertility of parent animals in rats. Except for minimal fetal effects at maternally toxic doses the prenatal, perinatal and postnatal development of the offspring was not affected.

Administration of NSAIDs (including diclofenac) inhibited ovulation in the rabbit and implantation and placentation in the rat, and led to premature closure of the ductus arteriosus in the pregnant rat. Maternally toxic doses of diclofenac were associated with dystocia, prolonged gestation, decreased fetal survival, and intrauterine growth retardation in rats. The slight effects of diclofenac on reproduction parameters and delivery as well as constriction of the ductus arteriosus in utero are pharmacologic consequences of this class of prostaglandin synthesis inhibitors (see sections 4.3 and 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetylcysteine
Mannitol (E421)
Sodium hydroxide
Water for injections
Propylene glycol
Benzyl alcohol

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened ampoules: 2 years

Once opened, use immediately and discard any unused contents.

Shelf life after dilution for IV infusion:
Intravenous infusions should be initiated immediately after preparing the infusion solutions (See section 6.6 Instructions for use/handling).
The infusion solutions should not be stored.

6.4 Special precautions for storage

Do not store above 25°C
Keep the ampoules in the outer container in order to protect from light.

6.5 Nature and contents of container

Diclac 25mg/ml solution for injection is contained in 3ml ampoules that are made of colourless neutral Type 1 Ph. Eur. glass.

Trays of 10 ampoules are packed in outer cardboard boxes.

Not all pack sizes may be marketed.

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

To be injected either intramuscularly by deep intragluteal injection into the upper outer quadrant or intravenously by slow infusion after dilution in accordance with the following instructions.

Each ampoule is for single use only. The solution should be used immediately after opening.

Once opened any unused solution should be discarded.

Only clear solutions should be used. If crystals or precipitates are observed, the infusion solution should not be used.

Intravenous use:
Depending on the intended duration of infusion (see section 4.2 Posology and method of administration), one ampoule should be diluted in 100 to 500 mL of isotonic saline (sodium chloride 0.9% solution) or glucose 5% and administered intravenously over a minimum of 30 minutes.

Buffer the normal saline or glucose 5% solution with sodium bicarbonate injectable solution (0.5 mL of 8.4% or 1 mL of 4.2% or a corresponding volume of a different concentration), before adding the Diclac ampoule.

A second dose may be administered 4-6 hours after the first infusion.

A maximum of two doses may be given intravenously.

7 MARKETING AUTHORISATION HOLDER

Rowex Limited,
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/009/010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 26 August 2007

10 DATE OF REVISION OF THE TEXT

October 2025