SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
DIKLORON 75 mg/3 ml Solution for IM Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ampoule (3 ml) contains:

Active substance:

Diclofenac sodium	75 mg

Excipients:

Mannitol	18 mg
Sodium metabisulphite	2 mg
Benzyl alcohol	120 mg
Propylene glycol	600 mg
Sodium hydroxide	0.82 mg

For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.
Almost colorless clear solution with a slight characteristic odor.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
It is indicated for the treatment of symptoms and signs of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis and treatment of acute gouty arthritis, acute musculoskeletal pain, post-operative pain and dysmenorrhea.

4.2 Posology and method of administration
Posology
As a general advice, the dose should be individually adjusted. Adverse effects should be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms.
The dose is usually one 75 mg ampoule daily, given by intragluteal injection into the upper outer quadrant. In severe cases (e.g. colic), the daily dose can exceptionally be increased to 2 injections of 75 mg, separated by an interval of a few hours (one into each buttock). Alternatively, 1 ampoule of 75 mg per day can be combined with other pharmaceutical forms of DIKLORON (e.g. tablets, suppositories) up to a total maximum daily dose of 150 mg.

Frequency and duration of administration
DIKLORON ampoules should not be given for more than 2 days. If necessary, treatment can be continued with DIKLORON tablets or suppositories.

Method of administration
Intramuscular injection is given by deep intragluteal injection into the upper outer quadrant.

Additional information on special populations
Pediatric population
Because of their dosage strength, DIKLORON ampoules are not suitable for children (see section 5.2). DIKLORON must not be given to premature babies or neonates. Benzyl alcohol may cause

toxic and anaphylactoid reactions in infants and children up to 3 years of age.

Geriatric population
Although the pharmacokinetics of DIKLORON are not impaired to any clinically relevant extent in elderly patients, non-steroidal anti-inflammatory drugs should generally be used with caution in such patients who are more prone to adverse reactions. It is recommended that the lowest effective dosage be used especially in frail elderly patients or those with a low body weight and the patient should be monitored against possibility of gastro-intestinal bleeding during NSAID therapy (see section 4.4).

Known cardiovascular disease or important cardiovascular risk factors
Treatment with DIKLORON is not recommended in patients with established cardiovascular disease or uncontrolled hypertension. If needed, patients with established cardiovascular disease or uncontrolled hypertension or significant risk factors for cardiovascular disease should be treated with DIKLORON only after careful consideration and only at doses ≤ 100 mg daily doses in case of prolonged treatment longer than 4 weeks (see section 4.4).

Renal impairment
DIKLORON is contraindicated in patients with renal failure (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 DIKLORON to patients with mild to moderate renal impairment (see section 4.4).

Hepatic impairment
DIKLORON is contraindicated in patients with 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 DIKLORON to patients with mild to moderate hepatic impairment (see section 4.4).

4.3 Contraindications
- In patients with known hypersensitivity to the active substance, sodium metabisulphite or to any of the other ingredients.
- In active gastric or intestinal ulcer, bleeding or perforation (see section 4.4 and 4.8)
- In the last trimester of pregnancy (see section 4.6)
- In hepatic failure
- In renal failure
- In ischemic heart disease, peripheral arterial disease, cerebrovascular disease and congestive heart failure (NYHA classification II-IV)
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), DIKLORON is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs drugs with prostaglandin-synthetase inhibiting activity (see sections 4.4 and 4.5).
  Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.
- It is contraindicated in the treatment of peri-operative pain in coronary artery bypass graft (CABG) surgery (see section “Special warnings and precautions for use”)
- In history of gastrointestinal bleeding or perforation, relating to NSAIDs therapy
- In active or history of recurrent peptic ulcer/ hemorrhage

4.4 Special warnings and precautions for use

Cardiovascular (CV) Risk:

- **NSAIDs may cause an increased risk of CV thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with CV disease or risk factors for CV disease may be at greater risk.**
- **DIKLORON Solution for IM Injection is contraindicated for treatment of peri-operative pain in coronary artery bypass graft (CABG) surgery.**

Gastrointestinal (GI) Risk:

- **NSAIDs cause an increased risk of serious GI undesirable effects including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These undesirable effects can occur at any time and with or without warning symptoms. Elderly patients are at greater risk for serious GI effects.**

General:

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

The concomitant use of DIKLORON 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 dosage be used in frail elderly patients or those with a low body weight (see section 4.2).

Like other NSAIDs including diclofenac, allergic reactions including anaphylactic/ anaphylactoid reactions may occur without previous exposure to the drug (see section 4.8 Undesirable Effects).

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

Gastrointestinal effects:

Gastrointestinal bleeding, ulceration or perforation, which can be fatal, has 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 DIKLORON, the medicinal product should be withdrawn.

The other factors increasing the risk of GI bleeding in patients receiving NSAID therapy include the use of oral corticosteroid or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and a poor general health status. As the most of the spontaneous reports regarding fatal GI events are associated with the elderly and debilitated patients, special care should be exercised in the treatment of these patients.

As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing DIKLORON in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see section 4.8). The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with hemorrhage or

perforation and in the elderly.

To reduce the risk of GI bleeding in patients with a history of ulcers complicated by bleeding or perforation and in the elderly, treatment should be initiated and continued at the lowest effective dose.

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

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 medications that could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, anti-platelet agents or selective serotonin-reuptake inhibitors (see section 4.5).

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

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

As with other NSAIDs, including diclofenac sodium, values of one or more liver enzymes may increase. Laboratory abnormalities may worsen, remain unchanged or be transient within continuation of the treatment. In clinical trials conducted with NSAIDs, significant increase (three times higher than upper limit of normal level or higher) in levels of ALT and AST about 1% of patients were reported. Additionally, severe hepatic reaction events, sometimes fatal, resulting in jaundice and fatal fulminant hepatitis, hepatic necrosis and hepatic impairment have been rarely reported, as well. During prolonged treatment with DIKLORON (e.g. tablets or suppository), 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, skin rash, etc.), DIKLORON treatment should be discontinued. Hepatitis may occur with the use of diclofenac sodium without prodromal symptoms. Caution is called for when using DIKLORON in patients with hepatic porphyria, since it may trigger an attack.

Renal effects:
Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a non-steroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at the greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

As fluid retention and edema 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 with diuretics or medicinal products that can significantly impact renal function, and in those patients with substantial extracellular volume depletion from any cause (e.g. before or after a major surgery) (see section 4.3). Monitoring of renal function is recommended as a precautionary measure when using DIKLORON in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

Advanced renal diseases:
No information is available from controlled studies regarding the use of DIKLORON in patients with advanced renal disease. Therefore, treatment with DIKLORON is not recommended in patients with advanced renal disease. If DIKLORON therapy is initiated, close monitoring of the patient's renal function is advisable.

Skin reactions:
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs, including DIKLORON (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy and reaction occurring in the majority of cases within the first month of treatment. DIKLORON should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

SLE and connective tissue diseases:
In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders, there may be an increased risk of aseptic meningitis.

Cardiovascular and cerebrovascular effects:
Treatment with diclofenac should be commenced only after a careful evaluation in patients with significant risk factors of cardiovascular events (e.g. hypertension, hyperlipidemia, diabetes mellitus, smoking etc.). This risk has been observed to increase, especially in high doses (150 mg daily) and long-term treatments. The lowest effective dose should therefore be used for the shortest possible duration in treatment with diclofenac. Health care professionals should regularly reevaluate the necessity of continuation of diclofenac treatment.

Clinical trials of several selective and non-selective COX-2 inhibitors of up to 3 years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction and stroke, which can be fatal. All NSAIDs, both COX-2 selective and non-selective may have a similar risk. Patients with known cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. Physician and patient should remain alert for the development of such events, even in the absence of previous cardiovascular symptoms. Patient should be informed about the signs and/or symptoms of serious cardiovascular events and the steps to take if they occur.

There is not consistent evidence that concurrent use of aspirin decreases the increased risk of serious cardiovascular thrombotic event associated with NSAID use. The concurrent use of aspirin with an NSAID increases the risk of serious GI events.

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see section "**Contraindications**").

Use of NSAIDs including diclofenac, particularly at high doses and in long-term treatment may be associated with a small increased risk of serious cardiovascular thrombotic events (including myocardial infarction or stroke).

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 warning. Patients should be instructed to see a physician immediately in case of such an event.

Hematologic effects:
Anemia is occasionally observed in patients using NSAIDs including DIKLORON. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis.
As with other NSAIDs, monitoring of blood count is advised during longer treatment with DIKLORON.
Like all NSAIDs, DIKLORON may inhibit platelet aggregation temporarily. Patients with defects of hemostasis 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 such as asthma exacerbations (so-called intolerance to analgesics/analgesics-asthma), Quincke's edema 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.

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, therefore DIKLORON should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Special precaution is required when DIKLORON is used parenterally because symptoms may be exacerbated in patients with bronchial asthma.

Anaphylactoid reactions:
As with other NSAIDs, in rare cases with diclofenac, allergic reactions including anaphylactic/anaphylactoid reactions may occur in patients without known prior exposure to the drug. DIKLORON should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or NSAIDs (see sections Contraindications and Special Warning and Precautions-**Asthma**). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Masking signs of infections:
Like other NSAIDs, DIKLORON may mask the signs and symptoms of infection due to its pharmacodynamic properties.

DIKLORON contains propylene glycol, which may cause alcohol-like reactions.
The presence of sodium metabisulphite can also lead to isolated hypersensitivity reactions and bronchospasm.

Female fertility:
The use of DIKLORON 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 DIKLORON should be considered.

Geriatric patients:
In geriatric patients, caution is indicated on basic medical grounds. In particular, it is recommended that the lowest effective dosage be used in frail elderly patients or those with low body weight.
DIKLORON cannot be expected to substitute for corticosteroid or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroid may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroid.

The pharmacological activity of DIKLORON in reducing [fever and] inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed non-infectious, painful conditions.

4.5 Interaction with other medicinal products and other forms of interaction
The concomitant use of DIKLORON with systemic NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided. The following interactions include those observed with DIKLORON Solution for IM 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 inhibition of diclofenac metabolism.

Lithium:
NSAIDs have produced an elevation of plasma lithium levels and reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity. 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 anti-hypertensive 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. 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 (see section 4.4).

Cyclosporine and tacrolimus:
In common with other NSAIDs, 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. 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.

Drugs known to cause hyperkalemia:
Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels. Serum potassium levels should therefore be monitored frequently (see section 4.4).

Quinolone derivatives 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:
Furosemide:
Clinical studies, and post-marketing observations, have shown that diclofenac can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (**Special warnings and precautions for use-Renal effects**), as well as to assure diuretic efficacy.

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

Other NSAIDs and corticosteroids:
Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects (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 DIKLORON affects the action of anticoagulants, there are isolated reports of an increased risk of hemorrhage in patients receiving DIKLORON and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Warfarin:
The effects of warfarin and NSAIDs on GI bleeding is synergistic; that is to say the risk of severe GI bleeding is higher in patients using these two medicines together when compared to patients using these medicines alone.

Aspirin:
When DIKLORON is used concomitantly with aspirin, rate of protein binding reduces while free

clearance of DIKLORON stays unchanged. Clinical significance of this interaction is unknown, and as with all other NSAIDs, concomitant administration of diclofenac and aspirin is not recommended as it may increase the possibility for risk of adverse events.

Selective serotonin reuptake inhibitors (SSRIs):
Concomitant administration of systemic NSAIDs including diclofenac sodium, 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 hypoglycemic and hyperglycemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Methotrexate:
NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate. Caution is recommended when NSAIDs including diclofenac are administered before or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity be increased.

Colestipol and cholestyramine:
These agents can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least 1 hour before or 4 to 6 hours after administration of colestipol/cholestyramine.

Mifepristone:
NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs 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 Pregnancy and Lactation
General Recommendation
Pregnancy category is C/D (3rd trimester).

Women of childbearing potential / Birth control (Contraception)
There are no data to suggest any recommendations for women of childbearing potential.

Pregnancy
There are insufficient clinical data regarding exposure in pregnancy for diclofenac sodium. Therefore, DIKLORON should not be used during the first two trimesters of pregnancy unless necessary (when the expected benefits to the mother outweigh the potential risks to the fetus).

As with other NSAIDs, diclofenac sodium has harmful pharmacological effects (e.g. possibility of uterine inertia and/or premature closure of the ductus arteriosus) during pregnancy and/or on fetus/newborn. Therefore, DIKLORON should not be used during the third trimester of pregnancy

(see section 4.3).

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

Reproductive ability/Fertility
Like other NSAIDs, use of DIKLORON may impair female fertility. It is not recommended for women attempting to conceive. Withdrawal of DIKLORON should be considered in woman who have difficulties conceiving or who are undergoing investigation of infertility.

4.7 Effects on ability to drive and use machinery
Patients experiencing visual disturbances, dizziness, vertigo, somnolence, or other central nervous system disturbances while using DIKLORON should refrain from driving or operating machinery.

4.8 Undesirable effects
Adverse drug reactions from clinical trials and/or spontaneous or literature cases are listed by MedDRA system order class. Within each system organ class, the adverse drug reactions are ranked frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III):

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (frequency cannot be estimated from the available data)

The following undesirable effects include those reported with diclofenac solution for IM 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 system disorders
Very rare: Thrombocytopenia, leucopenia, anemia (including hemolytic and aplastic anemia), agranulocytosis

Immune system disorders
Rare: Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock)
Very rare: Angioedema (including face edema)

Psychiatric disorders
Very rare: Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder

Nervous system disorders
Common: Headache, dizziness
Rare: Somnolence
Very rare: Paresthesia, memory impairment, convulsion, anxiety, tremor, meningitis aseptic, dysgeusia, cerebrovascular accident
Not known: Confusion, hallucination, disturbances of sensation, malaise

Eye disorders
Very rare: Visual impairment, blurred vision, diplopia
Not known: Optic neuritis

Ear and labyrinth disorders
Common: Vertigo
Very rare: Tinnitus, hearing impaired

Cardiac disorders
Very rare: Myocardial infarction, cardiac failure, palpitations, chest pain

Vascular disorders
Very rare: Hypertension, vasculitis

Respiratory, thoracic and mediastinal disorders
Rare: Asthma (including dyspnea)
Very rare: Pneumonitis

Gastrointestinal disorders
Common: Nausea, vomiting, diarrhea, dyspepsia, abdominal pain, meteorism, anorexia.
Rare: Gastritis, gastrointestinal hemorrhage, hematemesis, diarrhea hemorrhagic, melena, gastrointestinal ulcer (with or without bleeding or perforation), proctitis
Very rare: Colitis (including hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, esophageal disorder, intestinal diaphragm disease, pancreatitis, hemorrhoids

Hepatobiliary disorders
Common: Transaminases increased
Rare: Hepatitis, jaundice, liver disorder
Very rare: Fulminant hepatitis, hepatic necrosis, hepatic failure

Skin and subcutaneous tissue disorders
Common: Rash.
Rare: Urticaria.
Very rare: Bullous dermatitis, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, alopecia, photosensitivity reaction, purpura, Henoch-Schonlein purpura, pruritus.

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

Reproductive system and breast disorders
Very rare: Impotence

General disorders and administration site conditions
Common: Injection site reaction, pain and induration, and application site irritation
Rare: Edema, injection site necrosis

*The frequency reflects data from long-term treatment with a high dose (150 mg/day).

Description of selected adverse drug reactions

Arteriothrombotic events

Meta-analysis and pharmacoepidemiological data point towards a small increased risk of arteriothrombotic events (for example myocardial infarction) associated with the use of diclofenac, particularly at a high dose (150 mg daily) and during long-term treatment (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 the national reporting system.

4.9 Overdose and antidote

Symptoms

There is no typical clinical picture resulting from diclofenac overdose. Overdose can cause symptoms such as vomiting, gastrointestinal bleeding, diarrhea, 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 hemoperfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, acetic acid derivatives and related substances

ATC code: M01AB05

Mechanism of action

DIKLORON 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 diclofenac's mechanism of action. Prostaglandins play a major role in causing of 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

When used in rheumatic diseases, DIKLORON, with its anti-inflammatory and analgesic properties, significantly eliminates symptoms and findings such as pain, morning stiffness, and swelling in the joints that occur during rest and movement, and also improves function.

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

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

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

DIKLORON Solution for IM Injection is particularly suitable for initial treatment of inflammatory and degenerative rheumatic diseases, and of painful conditions due to inflammation of nonrheumatic origin.

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 2.5 µg/ml (8 µmol/L) are reached after about 20 minutes. The area under the concentration curve (AUC) after intramuscular administration is twice that following oral or rectal administration, because approximately half of the active substance is metabolized during the first passage through the liver (the "first-pass" effect) when administered orally or rectally.

The pharmacokinetic behavior is unchanged after repeated dosing. The drug does not accumulate when administered at the recommended dosing intervals.

Distribution:
Diclofenac is 99.7% protein bound, mainly to albumin (99.4%). The apparent volume of distribution is 0.12-0.17 L/kg.

Diclofenac enters the synovial fluid. Maximum concentrations are achieved in synovial fluid 2-4 hours after the peak plasma values have been attained. The half-life for elimination from the synovial fluid is 3-6 hours. 2 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 than in plasma for 12 hours.

Diclofenac was detected in a low concentration (100 ng/ml) in breast milk in one nursing mother. The estimated amount ingested by breastfed infant is equivalent to a 0.03 mg/kg/day dose.

Biotransformation:
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 (3'-hydroxy-, 4'-hydroxy-, 5-hydroxy-, 4',5-dihydroxy- and 3'hydroxy-4'-metoxy-diclofenac) 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. One metabolite (3'□hydroxy□4'□methoxy□ diclofenac) has a much longer plasma half□life. However, this metabolite is virtually inactive.

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 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 feces.

Linearity/Non-linearity:
The amount absorbed is in linear proportion to the size of the dose.

Characteristics in patients
Renal impairment:
In patients with renal failure, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics. When creatinine clearance is below 10 ml/min, calculated steady-state plasma levels of hydroxy metabolites are approximately four-fold higher than in normal subjects. However, the metabolites are eliminated via bile.

Hepatic impairment:
In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

Pediatric population:
Because of their dosage strength, DIKLORON Solution for IM Injection is not suitable for children and adolescents.

Geriatric population:
No age-related differences in the drug's absorption, metabolism or excretion have been observed.

Clinical studies:
DIKLORON is a product that has been used for a long time and has well-known clinical data.

5.3 Pre-clinical 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 had no influence on the fertility of parent animals in rats. The prenatal, perinatal and postnatal development of the offspring was not affected with the exception of minimal fetal effects at maternal toxic doses.

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 pharmacological results of this class of prostaglandin synthesis inhibitors (see sections 4.3 and 4.6).

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Mannitol
Sodium metabisulphite
Benzyl alcohol

Propylene glycol
Sodium hydroxide
Water for injection

6.2 Incompatibilities
As a rule, DIKLORON ampoules should not be mixed with other solutions for injection.

6.3 Shelf life
60 months.

6.4 Special precautions for storage
Store at room temperature below 25°C, protected from light.

6.5 Nature and contents of packaging
Type I, colorless glass ampoule of 3 ml in carton box of 4, 10 or 100.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Each ampoule is for single use only. The solution should be used immediately after opening. Any unused contents should be discarded.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

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10. DATE OF REVISION OF THE TEXT