SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DIKLORON 50 mg Enteric Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each enteric film coated tablet contains
Active substance:
Diclofenac sodium 50 mg

Excipient:
Lactose monohydrate (obtained from cow milk) 150 mg
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Enteric film coated tablet.
Round, slightly convex, white, film coated tablets embossed “d” on one side, with homogeneous appearance.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications
DIKLORON is indicated for the treatment of symptoms and signs of osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis and ankylosing spondylitis and treatment of acute gouty arthritis, acute musculoskeletal pains, post-operative pain and dysmenorrhea.

4.2 Posology and method of administration

Posology:
As a general recommendation, the dose should be individually adjusted. Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms.

Frequency and duration of administration
Adults
The recommended initial daily dosage is 100-150 mg. In milder cases, as well as for long-term therapy, daily 75-100 mg DIKLORON is usually sufficient.

The total daily dosage should generally be divided into 2 to 3 doses. To suppress nocturnal pain and morning stiffness, treatment with tablets during the day can be supplemented by the administration of a suppository at bedtime (up to a total maximum daily dose of 150 mg).

In primary dysmenorrhea, the daily dosage should be individually adjusted and is generally 50-150 mg. A dose of 50-100 mg should be given initially and, if necessary, increased over the course of several menstrual cycles up to a maximum of 150 mg/day. Treatment should be started upon appearance of the first symptoms and, depending on the symptomatology, continued for a few days.

Route of Administration
Tablets should be swallowed as a whole with liquids preferably before meal without breaking or chewing.

Additional information on special populations

Pediatric population
Due to its dosage, DIKLORON 50 mg Enteric Film Coated Tablets are not recommended in children.

Geriatric population
Although the pharmacokinetics of DIKLORON 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 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
Patients with congestive heart failure (NYHA I) or significant risk factors for cardiovascular disease (e.g., hypertension not controlled with medication) should only be treated with diclofenac after careful cardiovascular assessment. Since cardiovascular risks with diclofenac may increase with dose and duration of exposure, the lowest effective daily dose should be used for the shortest possible duration (see section 4.4).

Renal impairment
DIKLORON is contraindicated in patients with 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 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 or to any of the other ingredients
- Active gastric ulcer or intestinal ulcer, bleeding or perforation (see section 4.4 and 4.8)
- Last trimester of pregnancy (see section 4.6)
- Hepatic impairment (Child-Pugh class C) (liver and ascites cirrhosis)
- Renal impairment (GFR < 15 mL/min / 1.73 m^2)
- Established ischemic heart disease, peripheric arterial disease, cerebrovascular disease and congestive heart failure (NYHA classification II-IV)
- In inflammatory bowel disease (such as Crohn's disease or ulcerative colitis)
- Like other nonsteroidal anti-inflammatory drugs (NSAIDs), DICLORON is contraindicated in patients in whom bronchospasm, urticaria, nasal polyps, angioedema, allergy, and acute rhinitis

attacks have been triggered by the use of acetylsalicylic acid or other NSAIDs that inhibit the prostaglandin synthetase enzyme (see Sections 4.4 and 4.5). Severe, rarely fatal, anaphylaxis-like reactions to NSAIDs have been reported in these patients.
- It is contraindicated in treatment of postoperative pain in coronary artery bypass graft (CABG) surgery
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- Active or history of recurrent peptic ulcer/hemorrhage (two or more distinct episodes of proven ulceration or bleeding).

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 is contraindicated for treatment of post-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).

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

Gastrointestinal ulceration, bleeding, or perforation can occur at any time during treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), whether COX-2 selective or not, even in the absence of warning symptoms or a predisposing history. To minimize this risk, the lowest effective dose should be given for the shortest possible duration of treatment.

Placebo-controlled studies have shown an increased risk of thrombotic cardiovascular and cerebrovascular complications with some COX-2 selective inhibitors. It is not yet known whether this risk is directly related to the COX-1/COX-2 selectivity of individual NSAIDs. Since comparable clinical trial data for long-term treatment with the maximum dose of diclofenac are

currently unavailable, the possibility of a similarly high risk cannot be ruled out. Until such data are available, a careful risk-benefit assessment should be performed before using diclofenac in patients with clinically confirmed coronary heart disease, cerebrovascular disorders, peripheral arterial occlusive disease, or significant risk factors (e.g., hypertension, hyperlipidemia, diabetes, smoking). Because of this risk, the lowest effective dose should be given for the shortest possible duration of treatment.

The renal effects of NSAIDs include fluid retention with edema and/or arterial hypertension. Therefore, diclofenac should be used with caution in patients with heart failure and other conditions predisposing to fluid retention. Caution should also be exercised in patients receiving concomitant diuretics or ACE inhibitors, or in those at high risk of hypovolemia.

The consequences are generally more serious in the elderly. If gastrointestinal bleeding or ulceration occurs in patients treated with DICLORON, the medication should be discontinued.

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 NSAIDs therapy consist of use of corticosteroid or anticoagulants, prolonged NSAIDs therapy, smoking, use of alcohol, older age and a pure health condition. As the most of the spontaneous reports regarding fatal GI events are associated with the elderly and frail patients, special care should be exercised in 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, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with hemorrhage or perforation.

To reduce the risk of GI bleeding in patients with a history of ulcer, particularly if complicated with hemorrhage 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) 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 which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants such as warfarin, anti-platelet agents such as acetylsalicylic acid 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).

NSAIDs, including diclofenac, may be associated with an increased risk of gastrointestinal anastomotic leakage. Close medical supervision and caution are recommended when using diclofenac after gastrointestinal surgery.

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, diclofenac sodium can cause an increase in one or more liver enzymes. This has been observed very frequently in clinical studies with diclofenac (in approximately 15% of patients), but clinical symptoms have rarely occurred. Most of these cases involved insignificant increases. The increases observed frequently (in 2.5% of cases) were moderate (≥3 to <8 times the upper limit of normal), while the incidence of significant increases (≥8 times the upper limit of normal) remained around 1%. In the aforementioned clinical studies, elevated liver enzyme levels were accompanied by clinically evident liver damage in 0.5% of cases. Elevated enzyme levels were generally reversible after discontinuation of the drug. In addition, in rare cases, severe hepatic reactions, some of which were fatal, such as jaundice and fatal fulminant hepatitis, liver necrosis, and liver failure, have also been reported. During long-term treatment with DIKLORON (e.g., tablets or suppositories), regular monitoring of hepatic function is necessary as a preventive measure. If abnormalities in liver function tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if other findings (e.g., eosinophilia, skin rashes, etc.) appear, DIKLORON treatment should be discontinued. Hepatitis may occur with the use of diclofenac sodium without prodromal symptoms. Caution should be exercised when using DIKLORON in patients with hepatic porphyria, as an exacerbation may be triggered.

Renal Effects:
Because prostaglandins are important in maintaining renal blood flow, long-term treatment with high doses of NSAIDs, including diclofenac, frequently causes edema and hypertension (1-10%). Particular caution is required in patients with cardiac or renal dysfunction, a history of hypertension, elderly patients, patients receiving concomitant treatment with diuretics or medicinal products that may significantly affect renal function, and patients with significant extracellular volume loss for any reason (e.g., before or after major surgery) (see Section 4.3). In such cases where DIKLORON is used, monitoring of renal function is recommended as a precaution. Patients generally return to their pre-treatment status after discontinuation of treatment.

Since fluid retention and edema have been reported with NSAID therapy, including diclofenac, special caution is required in patients with a history of cardiac or renal dysfunction, hypertension, the elderly, those treated concomitantly with diuretics or medicinal products that significantly affect renal function, and those with significant extracellular volume depletion that may develop for any reason (e.g., before and after major surgery) (see Section 4.3). In such cases, when DIKLORON is used, monitoring of renal function is recommended as a preventive measure. The condition usually returns to the pre-treatment state after discontinuation of the drug.

Advanced Renal Diseases:
No information is available from controlled clinical studies regarding the use of DIKLORON in patients with advanced renal disease. Therefore, treatment with DIKLORON is not recommended in these 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, the onset of the 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.

Cardiovascular and Cerebrovascular Effects:
Diclofenac treatment should only be initiated after careful evaluation in patients with significant risk factors for cardiovascular events (e.g., hypertension, hyperlipidemia, diabetes mellitus, smoking). Since the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the lowest effective daily dose should be used for the shortest possible duration. Therefore, the shortest possible treatment duration and the lowest effective dose should be preferred in diclofenac treatment. Especially in treatments exceeding 4 weeks, healthcare professionals should regularly reassess the need for continued diclofenac treatment.

Patients with known cardiovascular disease or at risk of cardiovascular disease may be at higher risk. Even in the absence of previously observed cardiovascular symptoms, both the physician and the patient should be vigilant for the development of such events. The patient should be informed about the symptoms and/or signs of serious cardiovascular events and what to do if they occur.

Treatment with NSAIDs, including diclofenac, particularly at high doses and for long periods, may be associated with a small increase in serious cardiovascular thrombotic events (including myocardial infarction and stroke).

Patients should be alert for signs and symptoms of serious arteriothrombotic events that can occur without warning (e.g., chest pain, shortness of breath, weakness, slurred speech). Patients should be instructed to seek immediate medical attention in the event of such an event.

Hematologic Effects
As with other NSAIDs, blood count monitoring is recommended during long-term treatment with DICLORON.

Like other NSAIDs, DICLORON may temporarily inhibit platelet aggregation. Patients with hemostasis defects, bleeding diathesis, or hematological abnormalities should be carefully monitored.

Pre-existing Asthma:
In patients with asthma, seasonal allergic rhinitis, nasal mucosal swelling (e.g., nasal polyps), chronic obstructive pulmonary disease, or chronic respiratory system infections (especially those associated with allergic rhinitis-like symptoms), reactions such as asthma exacerbations (also called analgesic intolerance/analgesic asthma), Quincke's edema, or urticaria are more frequent with NSAIDs than in other patients. Therefore, special attention is advised for these patients (preparation for emergencies). This advice also applies to patients allergic to other substances, for example, those with skin reactions, itching, or urticaria.

Anaphylactoid Reactions
As with other nonsteroidal anti-inflammatory drugs (NSAIDs), allergic reactions, including anaphylactic/anaphylactoid reactions, may occur in rare cases with diclofenac, even without prior exposure to the drug.

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

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

Geriatric patients
In elderly patients, attention should be paid to basic medical principles. In particular, it is recommended to administer the lowest effective dose to elderly patients who are frail or of low body weight.

DIKLORON tablets contain lactose, and therefore patients with rare hereditary galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption problems should not use this medication.

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 tablets 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
When used together, diclofenac may increase plasma concentrations of lithium. Monitoring of serum lithium levels 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
Diclofenac, like other NSAIDs, can increase the nephrotoxicity of cyclosporine and tacrolimus due to its effect on renal prostaglandins. In these patients, diclofenac should be given at lower doses than in patients not taking cyclosporine or tacrolimus.

Drugs known to cause hyperkalemia
Concomitant treatment with potassium-sparing diuretics, cyclosporine, 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 seizures that may have resulted from the combined use of NSAIDs and quinolones.

Furosemide
Clinical studies, as well as 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 (see section 4.4), as well as to assure diuretic efficacy.

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 synergic; that is to say risk of severe GI bleeding is higher in patients using these two medicines together when compared to patients using these medicines alone.

Aspirin
As with other NSAIDs, the concomitant administration of diclofenac and aspirin is generally not recommended, as it increases the likelihood of adverse effects.

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.
Additionally, there is a risk of metabolic acidosis when administered concomitantly with diclofenac in patients with pre-existing renal impairment, as reported in isolated reports.

Methotrexate
Caution is advised when administering NSAIDs, including diclofenac, within 24 hours before or after methotrexate treatment, as this may increase methotrexate blood concentrations and toxicity.

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.

Mifepristone
NSAIDs should be administered 8 to 12 days after administration of mifepristone as NSAIDs reduces effects 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.

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

4.6 Fertility, pregnancy and lactation

General Recommendation
Pregnancy category is C (1st, 2nd trimester)
Pregnancy category is D (3rd trimester)

Women of child-bearing potential/Contraception
The use of DIKLORON may negatively affect female fertility and is not recommended for women trying to conceive. Women experiencing difficulty conceiving or undergoing infertility investigations should consider discontinuing the use of DIKLORON.

Pregnancy
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.

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and or 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 shown to result in increased pre-and post-implantation loss and embryo-fetal lethality.

In addition, an increased incidence of various malformations, including cardiovascular ones, has been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. Diclofenac should not be given during the first and second trimesters of pregnancy unless absolutely necessary. If diclofenac is used by a woman trying to conceive or during the first or second trimester of pregnancy, the dose should be low and the duration of treatment should be kept as short as possible.

Oligohydramnios/Neonatal Renal Failure:
Use of NSAIDs at approximately 20 weeks of gestation or later may cause impaired fetal renal function leading to oligohydramnios and, in some cases, neonatal renal failure. Although oligohydramnios has rarely been reported 48 hours after the start of NSAID treatment, these adverse outcomes typically occur days to weeks after treatment. Oligohydramnios is often, though not always, reversible upon discontinuation of treatment. Complications of prolonged oligohydramnios may include, for example, limb contractures and delayed lung maturation. In some post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusions or dialysis have been necessary. If DICLORON treatment exceeds 48 hours, consider ultrasound monitoring of the amniotic fluid. If oligohydramnios occurs, discontinue DICLORON and follow up according to clinical practice.

During the 3rd trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the fetus 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 the 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 labor

Consequently, DIKLORON is contra-indicated during the 3rd trimester of pregnancy.

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

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 who experience visual disturbances, drowsiness including dizziness, vertigo, somnolence or other central nervous system disturbances while taking DIKLORON should not drive and use

machines.

4.8 Undesirable effects
Adverse drug reactions from clinical trials and/or spontaneous reports and literature are listed according to the MeDRA system organ class. Within each system organ class, adverse drug reactions are listed in order of frequency, with the most frequent first. Within each frequency group, adverse drug reactions are listed in order of decreasing severity.
The following side effects were collected from clinical trials and spontaneously reported side effects with diclofenac:
Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); unknown (cannot be estimated from the available data)

The following undesirable effects include those reported with diclofenac tablets and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use:

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

Vascular disorders
Very rare: Hypertension
Very rare: Vasculitis

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

Gastrointestinal tract disorders
Common: Nausea, vomiting, diarrhea, dyspepsia, abdominal pain, flatulence, anorexia.
Rare: Gastritis, gastrointestinal hemorrhage, hematemesis, diarrhea hemorrhagic, melena, gastrointestinal ulcer (with or without bleeding - which can cause peritonitis with or without perforation).
Very rare: Colitis (including hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, esophageal disorder, diaphragm-like intestinal strictures, pancreatitis
Not known: Ischemic colitis

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: 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.
Not known: Drug rash with eosinophilia and systemic symptoms (DRESS)

Renal and urinary disorders
Common: Fluid retention, edema.
Very rare: Renal failure acute, hematuria, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, renal papillary necrosis.

Reproductive system and breast disorders
Very rare: Impotence

General disorders and administration site conditions
Rare: Edema

* 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).

Visual effects
Visual disturbances such as visual impairment, blurred vision, and diplopia can be among the effects of NSAIDs and are generally reversible after discontinuation of the drug. Inhibition of

prostaglandin synthesis and other related compounds that alter retinal blood flow can cause visual disturbances. If these symptoms occur during diclofenac treatment, an ophthalmological examination may be considered to rule out other causes.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is essential. It allows continued monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals should report any suspected adverse reaction via the national reporting system.

4.9 Overdose
Symptoms
There is no typical clinical picture resulting from diclofenac overdose, Over dosage can cause symptoms such as headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, diarrhea, dizziness, disorientation, excitation, coma, drowsiness, tinnitus, fainting 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 due to the high protein binding and extensive metabolism.
Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination (e.g. vomiting, gastric lavage) after ingestion of a potentially life- threatening overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Anti-inflammatory and anti-rheumatic products, non-steroidal anti-inflammatory drugs, acetic acid derivatives and related substances.
ATC code: M01AB05

Mechanism of action
DIKLORON contains diclofenac sodium, a nonsteroidal compound with pronounced anti-rheumatic, anti-inflammatory, analgesic, and antipyretic properties. As experimentally demonstrated, inhibition of prostaglandin biosynthesis is considered essential for diclofenac's mechanism of action. Prostaglandins play a major role in inflammation, pain, and fever.

In vitro, diclofenac sodium does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to those achieved in the human body.

Pharmacodynamic effects
DIKLORON used in rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac sodium elicit a clinical response characterized 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.
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.
In clinical trials diclofenac sodium has also been found to exert a pronounced analgesic effect in moderate and severe pain of non-rheumatic origin. Clinical studies have also revealed that, in primary dysmenorrhea, diclofenac sodium is capable of relieving the pain and reducing the extent of bleeding.

5.2 Pharmacokinetic properties

General properties
Absorption:
Diclofenac is completely absorbed from the enteric coated tablets after their passage through the stomach. Although absorption is rapid, its onset may be delayed due to the enteric coating of the tablet.
Mean peak plasma concentrations of 1.48 ±0.65 µg/ml (1.5 µg/ml = 5 µmol/ml) are attained on approximately 2 hours after ingestion of one 50 mg tablet.
The passage of a tablet through the stomach is slower when ingested with or after a meal than when it is taken before a meal, but the amount of diclofenac absorbed remains the same.
Since about half of diclofenac is metabolized during its first passage through the liver ("first pass" effect), the area under the concentration curve following oral or rectal administration is about half that following an equivalent parenteral dose.
Pharmacokinetic behavior does not change on repeated administration. No accumulation occurs provided the recommended dosage intervals are observed.

Distribution:
Diclofenac is 99.7% protein bound, mainly to albumin (99.4%). 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 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 infant consuming breast milk 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' hydroxyl-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 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 feces.

Linearity/Non-linearity:
The amount absorbed is linearly related to the dose strength.

Characteristics in patients
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 <10 ml/min, the calculated steady-state plasma levels of hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the 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:
The plasma level concentration attained in children following administration of equivalent doses (mg/kg body weight) is similar to the ones attained in adults.

Geriatric population**:**
No age-related differences have been observed in the absorption, metabolism, or excretion of the drug. In elderly patients, attention should be paid to basic medical principles. In particular, it is recommended that the lowest effective dose be given to elderly patients who are frail or of low body weight.

Clinical studies:
The clinical data of diclofenac is well-known since it has been in clinical use for many years.

5.3. Pre-clinical safety data
Preclinical data from acute and repeated dose toxicity studies and genotoxicity, mutagenicity, and carcinogenicity studies with diclofenac have shown no specific harm to humans at the recommended therapeutic doses.

The incidence of lymphoma (thymus) in mice and subcutaneous fibromas, fibroadenomas (mammary gland), or C-cell adenomas (thyroid gland) in rats were all within the laboratory control range for the animal strain used and were considered to have occurred incidentally.

In all toxicity studies in rats, hypertrophy of mesenteric lymph nodes or lymphadenitis with reactive hyperplasia was observed. These changes were accompanied by neutrophilia, which was also observed in studies in monkeys. These are presumed to be secondary reactions to ulcers observed in the gastrointestinal tract. In a two-year study, a dose-dependent increase in thrombotic vascular occlusions in the heart was observed in rats treated with diclofenac.

Further studies have shown that repeated oral doses (> 1 mg/kg body weight) of diclofenac cause effects affecting fertility in rats (low testosterone levels, decreased epididymal and testicular weight with histopathological changes). Similar effects were observed in the F1 generation following doses

≥ 1.25 mg/kg in a two-generation study. In dogs, a daily subcutaneous dose of 2 mg/kg diclofenac sodium resulted in increased spermatid count. Other studies have shown a decrease in mating frequency in female rats following repeated doses ≥ 0.5 mg/kg diclofenac. Therefore, its effect on both male and female fertility cannot be ruled out.

Diclofenac crosses the placental barrier in rodents. Administration of NSAIDs (including diclofenac) inhibited ovulation in rabbits and implantation and placentation in rats, causing premature closure of the ductus arteriosus in pregnant rats. In rats, maternally toxic doses of diclofenac were associated with dystocia, prolonged gestation, decreased fetal survival, and intrauterine growth retardation. The weak effects of diclofenac on both reproductive parameters and birth, as well as intrauterine ductus arteriosus constriction, are pharmacological consequences of the prostaglandin synthesis inhibitor class (see Sections 4.3 and 4.6).

In a study in mice, teratogenicity (cleft palate) was observed at a maternally toxic dose of 4 mg/kg. In rats and rabbits, doses up to the maternally toxic level did not lead to teratogenic effects. In a study in rabbits, delayed ossification and low fetal weight were the only changes observed in the studies.

At maternally toxic doses, perinatal and postnatal development of offspring was impaired (fertility, as well as birth weight and delayed postnatal growth).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate (obtained from cow milk)
Starch
Polyvinyl pyrolidone K25
Colloidal silicon dioxide
Talc
Magnesium stearate

Film coating
Polyethylene glycol 6000
Eudragit L-30-D-55
Talc
Simethicone Q7-2587

6.2 Incompatibilities
There are no known incompatibilities.

6.3 Shelf life
48 months

6.4 Special precautions for storage
Store at room temperature below 25°C. Protect from moisture.

6.5 Nature and contents of container
Blisters comprising of transparent PVDC on one side and printed aluminum foil on the other.
Each cardboard box contains 20 and 30 tablets.

6.6 Special precautions for disposal and other handling
Any unused material should be disposed according to local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No: 1
34303Küçükçekmece -ISTANBUL/TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER

144/61

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 24.05.1988
Date of last renewal :

10. REVISION DATE OF TEXT