SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE HUMAN MEDICINAL PRODUCT
DIKLORON SR 75 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains:
Active Substance:
Diclofenac sodium_____75 mg
Excipient(s) with known effect:
Sucrose_____75 mg
Lactose monohydrate (from bovine milk)_____0.98 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Sustained-release film-coated tablets.
White, round, slightly convex film-coated tablets with homogenous appearance.

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

4.2. Posology and method of administration
Posology
As a general recommendation, the dose should be individually adjusted. Adverse effects should be minimized by using the lowest effective dose for the shortest duration necessary.

Frequency and duration of administration
Adults
1 or 2 tablets of DIKLORON SR 75 mg per day, or a 100 mg dose of the product once a day is recommended. The maximum recommended daily dose is 150 mg. In milder cases, as well as for long-term therapy, 75 to 100 mg daily is usually sufficient.
Where the symptoms are most pronounced during the night or in the morning, DIKLORON SR should preferably be taken in the evening.

Route and method of administration
The tablets should be swallowed whole with liquid, preferably with a meal, and should not be divided or chewed.

Additional information on special populations
Pediatric population
Due to its dosage strength, DIKLORON SR is not suitable for children and adolescents.

Geriatric population
Although the pharmacokinetics of DIKLORON SR are not impaired to any clinically relevant extent in elderly patients, non-steroidal anti-inflammatory drugs (NSAIDs) should be used with particular caution in such patients who generally are more prone to undesirable effects. 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 uncontrollable by drug therapy) should be treated with diclofenac only after careful cardiovascular evaluation. 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 failure
DIKLORON SR in patients with severe renal failure (GFR <15 ml/min/1.73 m²) is contraindicated (see section 4.3). No specific studies were conducted in patients with renal failure; therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering DIKLORON SR to patients with mild to moderate renal failure (see section 4.4).

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

4.3. Contraindications
- Patients with known hypersensitivity to the active substance or to any of the excipients
- Active gastric and/or intestinal ulceration, hemorrhage or perforation (see sections 4.4 and 4.8)
- Last trimester of pregnancy (see section 4.6)
- Hepatic failure (Child-Pugh class C) (hepatic cirrhosis and ascites)
- Renal failure (GFR <15 ml/min/1.73 m²)
- Ischemic heart disease, peripheral arterial disease, cerebrovascular disease and congestive heart failure (NYHA classification II-IV)
- Like other non-steroidal anti-inflammatory (NSAID) drugs, diclofenac is contraindicated in patients with triggered attacks of bronchospasm, urticaria, nasal polyps, angioedema, allergy or acute rhinitis by the use of ibuprofen, 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.
- Post-operative pain treatment in coronary artery bypass graft (CABG) surgery (see section 4.4)
- History of gastrointestinal hemorrhage or perforation, related to NSAIDs therapy
- Active or history of recurrent peptic ulceration/hemorrhage (two or more distinct episodes of proven ulceration or 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 SR 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 SR 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, diclofenac may mask the signs and symptoms of infection due to its pharmacodynamic properties.

Gastrointestinal ulceration, bleeding or perforation may occur at any time during treatment with non-steroidal anti-inflammatory drugs (NSAIDs), whether COX-2 selective or not, even without warning symptoms or a relevant previous history. To minimize this risk, the lowest effective dose should be administered for the shortest possible duration.

Placebo-controlled studies have demonstrated that certain selective COX-2 inhibitors increase the risk of thrombotic cardiovascular and cerebrovascular complications. It is not yet known whether this risk correlates directly with the COX-1/COX-2 selectivity of the individual NSAIDs. Since no comparable clinical study data are currently available on diclofenac at maximum dosage during long-term therapy, the possibility of a similarly high risk cannot be ruled out. Until relevant data are available, diclofenac should be used in clinically confirmed cases of coronary heart disease, cerebrovascular disease, peripheral arterial occlusive disease, or in patients with significant risk factors (e.g. hypertension, hyperlipidemia, diabetes mellitus, smoking), only after careful consideration of the benefits and risks. The lowest effective dose should be administered for the shortest possible duration also because of this risk.

The renal effects of NSAIDs comprise fluid retention with edema and/or arterial hypertension. Diclofenac should therefore be used only with caution in patients with impaired cardiac function and other conditions that predispose them to fluid retention. Caution is also advised in patients taking diuretics or ACE inhibitors concomitantly, as well as in those with an increased risk of hypovolemia. In the elderly, the consequences are generally more serious. If gastrointestinal bleeding or ulceration occurs in patients on DIKLORON SR, treatment 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 SR, 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 SR 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, 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).

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 DIKLORON SR 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. This has been observed very frequently with diclofenac in clinical studies (in approximately 15% of patients), but is very rarely accompanied by clinical symptoms. Most of these cases involve borderline increases. Frequently (in 2.5% of cases) the increases observed were moderate (≥ 3 to < 8 times the upper limit of normal), while the incidence of marked increases (≥ 8 times the upper limit of normal) remained around 1%. Elevated liver enzyme levels were accompanied by clinically manifest liver damage in 0.5% of cases in the previously mentioned clinical studies. Elevated enzyme levels were generally reversible after discontinuation of the drug. Additionally, severe hepatic reaction events, sometimes fatal, resulting in jaundice and fatal fulminant hepatitis, hepatic necrosis and hepatic failure have been rarely reported, as well. During prolonged treatment with DIKLORON SR (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, rash, etc.), DIKLORON SR should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms. Caution is called for when using DIKLORON SR in patients with hepatic porphyria, since it may trigger an attack.

Renal Effects
Owing to the importance of prostaglandins in maintaining renal blood flow, prolonged treatment with high doses of NSAIDs, including diclofenac, frequently (1-10%) results in edema and hypertension. Particular caution is required in patients with impaired cardiac or renal function, in patients with a history of hypertension, in elderly patients, in patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in patients with substantial extracellular volume depletion from any cause (e.g. before or after major surgery) (see section 4.3). In such cases where DIKLORON SR is used, it is recommended to monitor renal function as a precaution. Patients usually return to their pre-treatment state after treatment is discontinued.

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 of 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 DIKLORON SR 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 clinical studies regarding the use of diclofenac in patients with advanced renal disease. Therefore, treatment with DIKLORON SR is not recommended in these patients with advanced renal disease. If DIKLORON SR 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 (Lyell's syndrome) and drug reaction with eosinophilia with systemic symptoms (DRESS) have been reported very rarely in association with the use of NSAIDs, including 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. DIKLORON SR should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

Cardiovascular and Cerebrovascular Effects
Treatment with diclofenac should be commenced only after a careful evaluation in patients carrying high risk of cardiovascular events (e.g. hypertension, hyperlipidemia, diabetes mellitus, smoking etc.). Because 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. The lowest effective dose should therefore be used for the shortest possible duration in treatment with diclofenac. Healthcare professionals should regularly re-evaluate the necessity of continuation of diclofenac treatment, especially for treatments exceeding 4 weeks.

Since fluid retention and edema have been reported in association with NSAID therapy, including diclofenac, patients with hypertension and/or mild to moderate congestive heart failure need to be followed appropriately and given appropriate advice.

Patients with known cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. Physicians and patients should remain alert for the development of such events, even in

the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of serious cardiovascular events and the steps to take if they occur.

Use of NSAIDs including diclofenac, particularly at high dose 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
As with other NSAIDs, monitoring of blood count is recommended during treatment with DIKLORON SR.

Like all NSAIDs, DIKLORON SR may inhibit thrombocyte aggregation temporarily. Patients with hemostasis defects 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 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.

Anaphylactoid Reactions
As with other non-steroidal anti-inflammatory drugs (NSAIDs), allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug.

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

Female fertility
The use of DIKLORON SR adversely affects female fertility and is not recommended for use in women trying to become pregnant. In women who have difficulty conceiving or who are undergoing investigation for infertility, discontinuation of DIKLORON SR 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.

DIKOLORON SR tablets contain lactose and thus patients with rare hereditary galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

DIKOLORON SR tablets contain sucrose and thus patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of DIKLORON SR with systemic NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided. The following interactions include those observed with DIKLORON SR tablets and/or other pharmaceutical forms of diclofenac.

Observed interactions to be considered:

Potent CYP2C9 inhibitors

Caution should be exercised when co-administering diclofenac with CYP2C9 inducers (such as rifampicin). This could lead to a significant decrease in plasma concentration and overexposure to diclofenac.

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 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 cyclosporine and tacrolimus due to the effect on renal prostaglandins. Therefore, diclofenac should be given at doses lower than those that would be used in patients not receiving 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 convulsions, which may have been due to concomitant use of quinolones and NSAIDs.

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 SR affects the action of anticoagulants, there are isolated reports of an increased risk of hemorrhage in patients receiving DIKLORON SR 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 all other NSAIDs, concomitant administration of diclofenac and aspirin is generally 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.

Additionally, isolated reports indicate a risk of metabolic acidosis following co-administration of diclofenac in patients with pre-existing renal impairment.

Methotrexate
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 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 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 worsen heart failure, decrease GFR, and increase plasma glycoside levels.

4.6. Fertility, pregnancy and lactation

General recommendation

The pregnancy category is “C” in the first two trimesters, but it is “D” in the last trimester.

Women of childbearing potential/Contraception

Since the use of DIKLORON SR may negatively affect female fertility, it is not recommended for use in women trying to become pregnant. Discontinuation of DIKLORON SR should be considered in women who have difficulty getting pregnant or who are being evaluated for infertility.

Pregnancy

As with other NSAIDs, diclofenac sodium has harmful pharmacological effects on pregnancy and/or the fetus/newborn (e.g. possible uterine inertia and/or premature closure of the ductus arteriosus).

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo-fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and/or heart malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. Based on the results of these studies, the absolute risk for cardiovascular malformation increased from less than 1% to approximately 1.5%. The risk is thought to increase with the dose and duration of treatment.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-fetal death.

In addition, increased incidence of various malformations, including cardiovascular, 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 clearly necessary. If diclofenac is used by a woman trying to conceive or during the first or second trimesters of pregnancy, the dose should be kept as low as possible and the duration of treatment should be as short as possible.

Oligohydramnios/Neonatal Renal Failure:

Use of NSAIDs from about 20 weeks gestation may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required. Consider ultrasound monitoring of amniotic fluid if DIKLORON SR treatment extends beyond 48 hours. If oligohydramnios occurs, discontinue DIKLORON SR and follow up according to clinical practice.

All prostaglandin synthesis inhibitors during the third trimester of pregnancy may expose the fetus to the following:

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)
- Renal dysfunction; it may progress to renal failure with oligohydramnios.

It may also expose the mother and newborn to the following conditions at the end of the pregnancy:
- Possible extension in bleeding time; an anti-platelet effect that can occur even at very low doses
- Inhibition of uterine contractions leading to delayed or prolonged labor

In conclusion, DIKLORON SR is contraindicated in the third trimester of pregnancy.

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

Reproductive ability / Fertility
Like other NSAIDs, use of DIKLORON SR may impair female fertility. It is not recommended for women attempting to conceive. Withdrawal of DIKLORON SR 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 machines
Patients experiencing visual disturbances, drowsiness including dizziness, vertigo, somnolence or other central nervous system disturbances while using DIKLORON SR should refrain from driving vehicles 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 (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: Angioneurotic edema (including facial edema)

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

Nervous system disorders
Common: Headache, dizziness
Rare: Somnolence, fatigue
Very rare: Paresthesia, memory impairment, convulsion, anxiety, tremor, meningitis aseptic, taste disturbances, 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, hypotension, 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, melena, gastrointestinal ulcer (with or without bleeding or perforation, which may lead to peritonitis)
Very rare: Colitis (including hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, esophageal disorder, intestinal diaphragm disease, pancreatitis
Not known: Ischemic colitis

The use of DICLORON SR may trigger chronic inflammatory diseases observed with pseudo-membranes and strictures in the small and large intestines.

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 reaction 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 (e.g. myocardial infarction or stroke) 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 may be among the effects of NSAIDs and are usually reversible after drug discontinuation. Inhibition of prostaglandin synthesis and other related compounds that alter retinal blood flow may cause visual impairment. If these symptoms occur during treatment with diclofenac, 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 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
Symptoms
There is no typical clinical picture resulting from diclofenac overdose. Overdose can cause symptoms such as headache, vomiting, epigastric pain, gastrointestinal hemorrhage, diarrhea, dizziness, drowsiness, 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 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: Antiinflammatory and antirheumatic products, non-steroids; Acetic acid derivatives and related substances
ATC code: M01AB05

Mechanism of action
DIKLORON SR 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 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
Diclofenac sodium 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, diclofenac sodium rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound edema.

DIKLORON SR is especially suitable for patients who need to use a dose of 75 mg per day. Taking it once a day facilitates especially long-term treatment and helps to prevent possible dosing errors. DIKLORON SR allows a maximum daily dose of 150 mg to be administered in a balanced manner, twice a day.

5.2 Pharmacokinetic properties

Absorption:
Judged by urinary recovery of unchanged diclofenac and its hydroxylated metabolites, the same amount of diclofenac is released and absorbed from diclofenac prolonged-release tablets as from gastro-resistant tablets. However, the systemic availability of diclofenac from diclofenac sodium prolonged-release tablets is on average about 82% of that achieved with the same dose of diclofenac administered in the form of gastro-resistant tablets (possibly due to release rate dependent “first-pass” metabolism). As a result of a slower release of the active substance from diclofenac sodium prolonged-release tablets, peak concentrations attained are lower than those observed following the administration of gastro-resistant tablets.

Mean peak concentration of 0.4 micrograms/mL (1.25 micromol/L) is reached on average 4 hours after ingestion of a prolonged-release (SR) tablet of 75 mg.

Food has no clinically relevant influence on the absorption and systemic availability of diclofenac sodium prolonged-release tablets.

On the other hand, mean plasma concentrations of 13 ng/mL (40 nmol/L) can be recorded at 16 hours after administration of diclofenac sodium 75 mg prolonged-release tablets.

Since approximately half of diclofenac is metabolized in its first pass through the liver ("first-pass" effect), the area under the concentration curve following oral administration is approximately half that obtained following parenteral administration of the same dose.

Trough concentrations are around 25 ng/mL (80 nmol/L) during treatment with diclofenac sodium prolonged-release tablets 75 mg twice daily.

Pharmacokinetic behavior does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed.

Distribution:
Diclofenac is bound to serum proteins at 99.7%, mainly to albumin (99.4%). The 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 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±56mL/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 much longer plasma half-life; however, this metabolite is almost 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 failure:
In patients with renal failure, 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 failure:
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 its dosage strength, DIKLORON SR is not suitable for children and adolescents.

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

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

5.3. Pre-clinical safety data
Non-clinical data from studies of safety pharmacology, acute toxicity and repeated dose toxicity as well as from genotoxicity, mutagenicity and carcinogenicity studies with diclofenac reveal no special hazard for humans at the intended therapeutic dosages.

The increased incidence of lymphoma (thymus) in mice, and the increased incidence of subcutaneous fibromas, fibroadenomas (mammary gland) or C-cell adenomas (thyroid) in rats, were all within the historical control range of the laboratory for the tested animal strain and were classified as coincidental.

All the toxicity studies performed on rats reported hypertrophy of the mesenteric lymph nodes or lymphadenitis with reactive hyperplasia. These changes were accompanied by neutrophilia, which was also observed in studies on monkeys. These reactions are suspected to be secondary to the ulcers observed in the gastrointestinal tract. In a 2-year study in rats treated with diclofenac, a dose-dependent increase in thrombotic vascular occlusions in the heart was reported.

Additional studies suggested that fertility was influenced (reduced testosterone levels and decreased epididymal and testicular weights combined with histopathological changes) in rats given repeated oral doses of diclofenac (>1 mg/kg body weight). Similar effects were also observed in the F1 generation after doses of ≥1.25 mg/kg in a 2-generation study. In dogs, a daily subcutaneous dose of 2 mg/kg diclofenac sodium resulted in an increased sperm count. Other studies report that the percentage of mating female rats was reduced following repeated diclofenac doses of ≥0.5 mg/kg. Hence, an influence on both male and female fertility cannot be ruled out.

Diclofenac crosses the placental barrier in rodents. The administration of NSAIDs (including diclofenac) inhibited ovulation in rabbits, implantation and placentation in rats, and premature closure of the ductus arteriosus in pregnant rats. In rats, maternal toxic doses of diclofenac were linked to dystocia, prolonged gestation, decreased fetal survival and delayed intrauterine growth. The minimal effects of diclofenac on reproduction parameters and birth, as well as on closure of the ductus arteriosus in utero, represent the pharmacological activity of this class of prostaglandin

synthesis inhibitors (see sections 4.3 and 4.6).

Teratogenicity (cleft palate) was observed at the maternal toxic dose of 4 mg/kg in a study of mice. No teratogenic effects were reported in rats and rabbits treated with doses up to the maternal toxic level. Delayed ossification and reduced fetal weight in one study of rabbits were the only changes observed in these tests.

At maternal toxic doses, perinatal and postnatal development of the progeny was adversely affected (fertility, as well as birth weight and delayed postnatal growth).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sucrose
Hydroxypropyl methylcellulose 4000 SR
Colloidal silicon dioxide
Polyvinylpyrolidone K25
Polyethylene glycol 6000
Magnesium stearate
Opadry White OY-LS-28913
HPMC 2910/ Hypromellose 15cP (E464)
Titanium dioxide (E171)
Lactose monohydrate (from bovine milk)
Macrogol/PEG 4000 (E1521)

6.2. Incompatibilities

There are no known incompatibilities.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at room temperature below 25ºC.

6.5. Nature and contents of container

Blisters covered with transparent PVC/PVDC on one side and printed aluminum foil on the other. Each cardboard box contains 10 tablets.

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.

7. MARKETING AUTHORIZATION HOLDER

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

8. MARKETING AUTHORIZATION NUMBER

2015/260

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 11.03.2015
Date of last renewal :

10. DATE OF REVISION OF THE TEXT