SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE HUMAN MEDICINAL PRODUCT
DIKLORON® 100 mg Retard Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains:

Active Substance:
Diclofenac Sodium_____100 mg

Excipient(s) with known effect:
Sucrose_____100 mg
Lactose monohydrate

For the full list of excipients, see. 6.1

3. PHARMACEUTICAL FORM
Prolonged release tablet.
Round, slightly convex, white, film-coated tablets with homogenous appearance.

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 for the 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 adjusted individually. Adverse effect symptoms should be minimized by using the lowest effective dose for the shortest duration necessary.

Frequency and duration of administration
Adults
The recommended initial daily dose is 100-150 mg (administered as 1 tablet of DIKLORON Retard or 2 tablets of DIKLORON SR 75 mg Film Coated Tablets (other dosage strength of the product)).

In milder cases, as well as for long-term therapy, 75-100 mg daily would generally be sufficient. The recommended maximum daily dose is 150 mg.

Where the symptoms are most pronounced during the night or in the morning, DIKLORON should preferably be administered in the evening.

Route of Administration
The tablets should be swallowed as whole with liquids, preferably before a meal, and should not be divided or chewed.

Additional information on special populations
Pediatric population
Due to its dosage strength, DIKLORON 100 mg Retard Film Coated Tablets are not recommended for children and adolescents.

Geriatric population (65 years and over)
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
Treatment with DIKLORON is not recommended in patients with known cardiovascular disease or uncontrollable hypertension. If necessary, patients with known cardiovascular disease or uncontrollable hypertension or important risk factors for cardiovascular diseases should only be treated with DIKLORON following an attentive evaluation and only with ≤100 mg doses in case of treatment lasting longer than 4 weeks (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 or intestinal ulcer, bleeding or perforation (see section 4.4 and 4.8)
- Last trimester of pregnancy (see section 4.6)
- Hepatic failure
- Renal failure
- Established 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 section 4.4). Severe, rarely fatal, anaphylactic-like reactions have been reported in these patients.
- Contraindicated in therapy of peri-operative 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

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 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).

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 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, 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. 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, rash, etc.), DIKLORON should be discontinued. Hepatitis may occur with use of diclofenac 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 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 were reported in association with NSAID therapy, incl. 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 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 clinical studies regarding the use of diclofenac 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 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 should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

SLE and connective tissue diseases
Risk of aseptic meningitis may increase in patients with systemic lupus erythematosus (SLE) and mixed connective tissue diseases.

Cardiovascular and cerebrovascular effects
Treatment with diclofenac should be commenced only after a careful evaluation in patients carrying high cardiovascular events risk (e.g. hypertension, hyperlipidemia, diabetes mellitus, smoking etc.). In particular, this risk increases at high doses (150 mg daily) and in long-term treatment. The lowest effective dose should therefore be used for the shortest possible time in treatment with diclofenac. Healthcare personnel should regularly reassess the necessity of diclofenac treatment's continuation.
Clinical trials of several selective and non-selective COX-2 inhibitors of up to three 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 does increase 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 4.3).
Use of NSAIDs including diclofenac, particularly at high dose (150 mg daily) 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 can be associated with that the effect is not literally defined following water retention, hidden or gross GI blood loss or erythropoiesis.
As with other NSAIDs, monitoring of blood count is advised during treatment with DIKLORON.
Like all NSAIDs, DIKLORON 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.
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 recommended when DIKLORON is used parenterally because symptoms may be exacerbated in patients with bronchial asthma.

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. DIKLORON should not be given to patients with the aspirin triad. This symptom complex is typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see sections 4.3 and 4.4-Asthma). Emergency help should be sought in cases where an anaphylactic reaction occurs.

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 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.

DIKLORON's pharmacological activity in reducing (fever and) inflammation may diminish utility of these diagnostic signs in detecting complications of presumed non-infectious, painful conditions.

DIKOLORON Retard tablets contain lactose and thus patients with rare hereditary galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption must not use this medicine.

DIKOLORON Retard 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 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
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 cyclosporine 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 cyclosporine. 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, 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.

<u>Anticipated interactions to be considered:</u>
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 - Renal Effects), 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
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 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.

4.6. Fertility, pregnancy and lactation
General recommendation
Pregnancy category is C/D (3rd trimester).

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

Pregnancy
There are insufficient clinical data regarding exposure to diclofenac in pregnancy. Therefore, DIKLORON should not be used during the first two trimesters of pregnancy unless clearly necessary (the expected benefits to the mother outweigh the 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. DIKLORON should therefore not be used during the third trimesters of pregnancy (see section 4.3).

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.

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 not drive and use machines.

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

The following undesirable effects include those reported with diclofenac retard tablets 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 (incl. 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 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 or perforation)
Very rare: Colitis (including hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, esophageal disorder, intestinal diaphragm disease, pancreatitis

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

Renal and urinary disorders
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
Common: Injection site reaction, pain and induration, application site irritation
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).

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 in accordance with local requirements.

4.9. Overdose
Symptoms
There is no typical clinical picture resulting from diclofenac overdose. Overdose can cause symptoms such as vomiting, 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 potentially toxic overdose ingestion and gastric decontamination (e.g. vomiting, gastric lavage) after potentially life-threatening overdose ingestion.

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 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

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.

DIKLORON Retard is particularly suitable for patients in whom a daily dose of 100 mg is appropriate to the clinical picture. Possibility of prescribing the medicinal product in a single daily dose considerably simplifies long-term treatment and helps to avoid possibility of dosage errors.

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 DIKLORON Retard as from gastro-resistant tablets. However, the systemic availability of diclofenac from DIKLORON Retard 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 DIKLORON Retard, peak concentrations attained are lower than those observed following the administration of gastro-resistant tablets.

Mean peak concentration of 0.5 µg/ml (1.6 µmol/L) is reached on average 4 hours after ingestion of a prolonged-release tablet of 100 mg.

Food has no clinically relevant influence on the absorption and systemic availability of DIKLORON Retard.

On the other hand, mean plasma concentrations of 13 ng/ml (40 nmol/L) can be recorded at 16 hours after administration of DIKLORON Retard 100 mg.

Since about half of diclofenac is metabolized during its first passage through the liver ("first pass" effect), the area under the concentration curve (AUC) following oral administration is about half that following an equivalent parenteral dose.

Trough concentration is around 22 ng/ml (70 nmol/L) during treatment with DIKLORON Retard 100 mg once daily.

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

Distribution

Diclofenac binds to serum proteins at a rate of 99.7%, primarily to albumin (99.4%). The virtual 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. 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 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, metabolites are ultimately cleared through 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 its dose strength, DIKLORON Retard is not suitable for children and adolescents.

Geriatric population
No relevant age-dependent difference in drug's absorption, metabolism, or excretion were observed.

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, 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, or intrauterine growth retardation in rats. Slight effects of diclofenac on reproduction parameters and delivery as well as constriction of the ductus arteriosus in utero are pharmacologic consequences of this class of prostaglandin synthesis inhibitors (see sections 4.3 and 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Hydroxypropyl methylcellulose 4000 SR
Colloidal silicon dioxide
Polyvinyl pyrolidone K25
Polyethylene glycol 6000
Sucrose
Magnesium stearate
Film coating agents: Opadry White OY-LS-28913
- HPMC 2910 / Hypromellose 15cP
- Titanium dioxide
- Lactose monohydrate
- Macrogol / PEG 4000

6.2. Incompatibilities

There are no known incompatibilities.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store at room temperature below 25ºC. Protect from moisture.

6.5. Nature and contents of container

Blisters with transparent PVC/PVDC foil on one side and printed aluminum foil on the other side. Each cardboard box contains 10 or 30 film-coated 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
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER

167/34

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 27.12.1993
Date of last renewal : 04.01.2013

10. REVISION DATE OF TEXT