SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Diclonova 50mg/100 mg suppositories

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One suppository contains the active substance 50mg/100 mg diclofenac sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suppositories, white bullets shaped

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diclonova 50mg/100 mg suppositories is used for the symptomatic treatment of inflammatory and degenerative forms of rheumatism in the musculoskeletal system such as rheumatoid arthritis, spondylitis, including ankylosing spondylitis, osteoarthritis, nonarticular rheumatism (e.g. tendonitis, tenosynovitis, bursitis, frozen shoulder, tennis elbow). For the treatment of painful vertebral syndromes, acute attacks of gout, acute backache, for the treatment of posttraumatic and post-operative pain, inflammation, and swelling (e.g. following dental or orthopaedic surgery). For the treatment of toothache and auxiliary treatment of painful conditions in gynaecology (e.g. primary dysmenorrhoea). Further to treat migraine attacks and acute renal colic.

Diclonova 50mg/100 mg suppositories is indicated in adults.

4.2 Posology and method of administration

Posology Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4). In long-term treatment with diclofenac, the renal and hepatic function and blood count must be monitored.

Adults: The recommended daily dose is 100 mg. The maximum daily dose is 150 mg. To achieve the maximum daily dose, where necessary, 100 mg suppository may be combined with avaible 50 mg suppository or 50 mg tablet up to the maximum dose of 150 mg a day. Preferably, 100 mg suppository should be inserted into the rectum at bedtime and 50 mg tablet should be used in the morning after breakfast.

Paediatric population Diclonova-100 mg suppositories should not be used in children and adolescents below 18 years of age because of the amount of active substance contained per suppository.

Special populations Elderly Diclonova 50mg/100 mg suppositories should be used with particular caution in elderly who are generally more prone to adverse reactions, especially gastrointestinal bleeding and perforation (see section 4.4). In particular the lowest effective dosage should be used and the patient should be monitored during the therapy.

Renal and/or hepatic impairment Caution is advised in patients with impaired renal and/or hepatic function, and in particular the lowest effective dosage should be used. Monitoring of renal and/or hepatic function is recommended as a precautionary measure when using diclofenac in such cases (see section 4.4). Diclonova 50mg/100 mg suppositories is contraindicated in patients with severe renal and/or hepatic failure (see section 4.3).

Method of administration for rectal administration only. Not to be taken by mouth. The suppository should be inserted well into the rectum, preferably at bedtime.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1. Patients with previously shown hypersensitivity reactions (e.g. bronchospasm, asthma, angioedema, urticaria, or acute rhinitis) in response to other NSAIDs or acetylsalicylic acid. Last trimester of pregnancy (see section 4.6). Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disorder, severe heart failure. Renal or hepatic failure (see section 4.4). Active gastrointestinal bleeding, ulceration, perforation. History of gastrointestinal bleeding or perforation related to previous NSAIDs therapy. Active, or history of recurrent peptic ulcer/bleeding or perforation (two or more distinct episodes of proven ulceration or bleeding). Proctitis.

4.4 Special warnings and precautions for use

General Adverse reactions may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms. The concomitant use of diclofenac with systemic NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects. Caution is necessary in the elderly patients with frail medical grounds and with a low body weight. There is increased incidence of side effects, especially gastrointestinal bleeding and perforation, which may be fatal. Furthermore, impaired renal, hepatic and heart function may occur. It is recommended that the lowest effective dose should be used in elderly patients. As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur with diclofenac without earlier exposure to the drug. Like other NSAIDs, diclofenac may mask the signs and symptoms of the infection due to its pharmacodynamics properties. This medicinal product should not be used in children and adolescents below 18 years of age due to the amount of active ingredient per suppository.

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 diclofenac, the medicinal product should be withdrawn. As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing diclofenac in patients with symptoms indicative of gastrointestinal disorders, in patients with history of gastrointestinal ulceration, bleeding or perforation (see section 4.8). The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAID doses including diclofenac, and in patients with a history of ulcer, particularly if complicated with bleeding or perforation (see section 4.3).

The elderly have increased frequency of adverse reactions, especially gastrointestinal bleeding and perforation which may be fatal (see section 4.8). To reduce the risk of gastrointestinal toxicity in patients with a history of ulcer, particularly if complicated with bleeding 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. misoprostol or proton pump inhibitors) should be considered in these patients, and also in patients requiring concomitant treatment with low dose acetylsalicylic acid or medicinal products likely to increase gastrointestinal risk (see section 4.5). Patients with a history of gastrointestinal toxicity, particularly when elderly, must be notified to report any unusual gastrointestinal symptoms (especially gastrointestinal bleeding), especially at the beginning of therapy. Caution is recommended in patients receiving concomitant medications which may increase the risk of ulceration or bleeding [e.g. oral systemic corticosteroids, anticoagulants such as warfarin, SSRIs or anti-platelet agents such as acetylsalicylic acid (see section 4.5)]. Close medical surveillance and caution should be exercised in patients with ulcerative colitis or with Crohn's disease as these conditions may be exacerbated by this therapy (see section 4.8).

Cardiovascular and cerebrovascular effects It is necessary to monitor and instruct patients with a history of hypertension and/or mild to moderate congestive heart failure, because there have been reported fluid retention and oedema in association with the treatment with NSAID. Clinical trial and epidemiological data indicate a mild increasing risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (150 mg daily) and in long-term treatment. Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking) should only be treated with diclofenac after careful consideration. As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to treatment should be evaluated regularly.

Hepatic effects Close medical surveillance is required when prescribing Diclonova 50mg/100 mg suppositories to patients with impairment hepatic function, as their condition may be exacerbated. As with all NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with diclofenac, 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), therapy of diclofenac should be discontinued. Hepatitis may occur with

Diclofenac without prodromal symptoms. Caution is necessary when using diclofenac in patients with hepatic porphyria, since it may trigger an attack.

Renal effects in association with NSAIDs therapy, including diclofenac, there have been reported fluid retention and oedema. Particular caution is necessary in patients with impaired cardiac or renal function, history of hypertension, in 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 diclofenac in such cases. After discontinuation of the therapy, the values usually recover to the pre-treatment state.

Haematological effects as with other NSAIDs, monitoring of the blood count is recommended. Like other NSAIDs, diclofenac may reversibly inhibit platelet aggregation. Patients with disorders of hematopoiesis and coagulation should be carefully monitored.

Skin effects 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). These reactions are most at risk for patients in early treatment, the beginning of the reaction is most common during the first month of treatment. Therapy of diclofenac should be discontinued at the first appearance of skin rash, mucosal lesions, or any other signs of hypersensitivity.

Asthma In patients with asthma, seasonal allergic rhinitis, nasal polyps, chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially rhinitis-like symptoms), reactions on NSAIDs such as asthma-like exacerbations (so called intolerance to analgesics/analgesics asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria.

4.5 Interaction with other medicinal products and other forms of interaction

Potent CYP2C9 inhibitors (e.g. voriconazole, fluconazole, sulfinpyrazone): Concomitant use may cause increase maximum plasma concentrations and exposure to diclofenac.

Lithium, digoxin: If used concomitantly, diclofenac may raise their plasma concentrations. Monitoring of their serum levels is recommended.

Diuretics and antihypertensive agents (e.g. beta-blockers, ACE inhibitors): If used concomitantly, diclofenac may cause a decrease in their antihypertensive effect, therefore dosage of antihypertensive drugs should be regulated, blood pressure should be monitored (especially in the elderly), and patients should be adequately hydrated. Consideration should be given to monitoring of renal function, especially if diclofenac is concomitantly administered with diuretics and ACE inhibitors, due to the increased risk of nephrotoxicity. Concomitant treatment with potassium-

sparing diuretics may be associated with hyperkalemia, which should therefore be frequently monitored.

Other NSAIDs and corticosteroids: Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of undesirable effects and gastrointestinal bleeding (see section 4.4).

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding. Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

SSRIs: Concomitant administration of systemic NSAIDs, including diclofenac, and SSRIs may increase the risk of gastrointestinal bleeding [inhibition of platelet aggregation, and gastrointestinal mucosal disorder (see section 4.4)].

Antidiabetics: During the concomitant administration of diclofenac with antidiabetics, the clinical effect of antidiabetics is not influenced. However, there have been isolated reports of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of blood glucose levels is recommended as a precautionary measure during the concomitant therapy.

Methotrexate: If used concomitantly, plasma concentrations of methotrexate may rise and the toxicity may increase. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before or after treatment with methotrexate. For this reason, monitoring of the blood count during first week of treatment with diclofenac and methotrexate is recommended as a precautionary measure during concomitant administration. Isolated cases of pancytopenia were also recorded in concomitant administration of NSAIDs and methotrexate.

Ciclosporin: If used concomitantly, diclofenac may increase the nephrotoxicity of ciclosporin due to renal prostaglandins inhibition. In combination therapy, diclofenac should be used at lower doses.

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

Quinolone antibacterials: If used concomitantly, the convulsions may occur. This may occur in patients with or without a previous history of epilepsy or convulsions.

Colestipol and cholestyramine: Colestipol or cholestyramine 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 their administration.

4.6 Fertility, pregnancy and lactation

Pregnancy Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1 % up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo/foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during organogenetic period. During the first and second trimester of pregnancy, diclofenac should not be administered unless it is absolutely necessary. If diclofenac is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to: - cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension), - renal dysfunction, which may progress to renal failure with oligo-hydramniosis. 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 labour.

Consequently, diclofenac is contraindicated during the third trimester of pregnancy.

Breastfeeding Like other NSAIDs, diclofenac and its metabolites pass into breast milk in small amounts. Therefore, diclofenac should not be administered during breast feeding in order to avoid undesirable effects in the infant.

Fertility Diclofenac may impair female fertility and is not recommended in women attempting to conceive. Impairment is reversible and resolves after termination of therapy. In women who may have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of diclofenac should be considered.

4.7 Effects on ability to drive and use machines

In some diclofenac treated patients visual disturbances, dizziness, vertigo, headache or headedness, fatigue, somnolence, lassitude or other CNS disturbances may occur. In these circumstances patients should not drive, operate machines, and perform other activities requiring increased attention.

4.8 Undesirable effects

Adverse reactions are listed by system organ classes based on frequency using the following convention: 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). Within each frequency category, undesirable effects are presented in order of decreasing seriousness.

The following adverse reactions include long-term and short-term use.

Blood and lymphatic system disorders Very rare Agranulocytosis, anemia (including haemolytic and aplastic anemia), thrombocytopenia, leukopenia.

Immune system disorders Rare Hypersensitivity, anaphylactic and anaphylactoid reactions including hypotension and shock. Very rare Angioedema including face oedema.

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

Nervous system disorders Common Headache, dizziness. Rare Somnolence. Very rare Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.

Eye disorders Very rare Visual impairment, blurred vision, and diplopia.

Ear and labyrinth disorders Common Vertigo. Very rare Tinnitus, hearing impaired. Cardiac disorders Very rare Palpitations, chest pain, cardiac failure, myocardial infarction.

Vascular disorders Very rare Hypertension, vasculitis.

Respiratory, thoracic and mediastinal disorders Rare Asthma including dyspnoea. Very rare Pneumonitis.

Gastrointestinal disorders Common Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia. Rare Gastritis, gastrointestinal bleeding, haematemesis, melaena, diarrhoea haemorrhagic, gastrointestinal ulcer (with or without bleeding or perforation), proctitis. Very rare Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis. Not known: Ischaemic 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, loss of hair, photosensitivity reaction, purpura including allergic purpura, Henoch-Schonlein purpura, pruritus.

Renal and urinary disorders Very rare acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.

General disorders and administration site conditions Common Application site irritation. Rare Oedema.

The most commonly observed adverse events are gastrointestinal. Gastrointestinal bleeding may be sometimes fatal, particularly in the elderly (see section 4.4). Clinical trial and epidemiological data

consistently point towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (150 mg daily) and in long-term treatment (see section 4.3 and 4.4).

Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 **Overdose**

Symptoms There is no typical clinical manifestation resulting from diclofenac overdosage. Over dosage can cause symptoms such as nausea, vomiting, gastrointestinal bleeding, diarrhoea, convulsions, tinnitus, dizziness, headedness and headache, fatigue, somnolence, hallucinations, anxiety, tendency to oedema. In the event of significant poisoning, acute renal failure and liver damage are possible.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinflammatory and antirheumatic products, non-steroids.

Diclofenac sodium is a derivate of phenylacetic acid. It is a non-steroidal anti-inflammatory and antirheumatic drug (NSAID) that is used as an analgesic and antiphlogistic with anti-oedematous and antipyretic effect. The mechanism of action of diclofenac sodium is inhibition of the cyclooxygenase enzyme, which causes the synthesis of prostaglandins and other mediators of inflammation, pain and fever. Diclofenac positively affects the synthesis of the macromolecules of the connective tissue and inhibits platelet aggregation. In rheumatic disorders and post-traumatic and postoperative conditions diclofenac reduces morning stiffness, pain at rest, pain on movement and reduces oedema.

5.2 **Pharmacokinetic properties**

Absorption Diclofenac is completely absorbed after peroral or rectal administration. Absorbed amount is linearly related to the dose. Plasma concentrations are derived to administrated dose. Maximal plasma concentrations after administration of suppositories are attained after 30 minutes. 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. In rectal administration, the first-pass effect can be of a lesser extent. Pharmacokinetic behaviour does not change on repeated administration. Accumulation does not occur, provided the recommended dosage intervals are observed.

Distribution the diclofenac is 99.7 % plasmatic protein bound, mainly to albumin (99.4 %). The volume of distribution of diclofenac is 0.12 to 0.17 l/kg. Diclofenac passes into the synovial fluid, where the highest concentrations are attained in 2-4 hours after attaining maximum plasma concentration. The mean terminal half-life of diclofenac is 5 hours. Two hours after attaining maximum plasma concentration, concentration of the active substance is already higher in the synovial fluid than in the plasma, and remains higher for up to 12 hours.

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, most of which are converted to glucuronide conjugates. Two phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.

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

Linearity/non-linearity absorbed amount is linearly related to the dose. Patient age has no influence on the absorption, metabolism and excretion.

In patients with renal damage, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. The elimination rate of diclofenac metabolites, however, may be up to four times reduced. There are no relevant data on diclofenac kinetics in repeated administration in renal insufficiency. In patients with chronic hepatitis the kinetics and metabolism of diclofenac are the same as in patients without liver disease. Pharmacokinetic parameters were significantly different in the patients with alcoholic cirrhosis.

5.3 **Preclinical safety data**

New preclinical safety studies have not been performed. Non-clinical studies revealed genotoxic potential of diclofenac to somatic and germinal cells of mice. This effect was observed after 13 weeks of the treatment with dose 3.5 mg/kg. No signs were observed after 4 weeks. Experimental studies with prokaryotes (Salmonela typhimurium and Bacillus subtilis) suggested this genotoxic potential only in one test method, the others were negative. Studies on animals revealed potential teratogenic and developmental toxic effect of diclofenac on rat embryos and Xenopus laevis, which were observed after higher concentrations, than are achived after administration of 100 mg suppository in human. The AUC based on free diclofenac was 4x higher in pregnant female rats than in non-pregnant. The difference is considered to be due to a lower concentration of serum albumin and a higher concentration of non-esterified fatty acid that inhibits drug binding to albumin, in pregnant rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Diclofenac sodium, Peg 1500, Peg 6000 and Glycerin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30 °C, in the original package, in order to protect from light.

6.5 Nature and contents of container

Printed Strip Film (58mm), Packing size: 20 strips x 5 suppositories

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed off in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

PL/SmPC/22-1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14TH September, 2019

10. DATE OF REVISION OF THE TEXT

August, 2022