

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCTS

CLODIFEN 100 mg Suppositories

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug Substance:

Each suppository contains 100 mg of Diclofenac sodium.

Excipients:

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suppository

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Exacerbation of inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, spondylarthritis, painful syndromes of the vertebral column, non-articular rheumatism,
- Acute gout attacks,
- Post-traumatic and post-operative pain, inflammation and swelling; e.g. following dental or orthopedic surgery.
- Painful and/or inflammatory conditions in gynecology; e.g. primary dysmenorrhea or adnexitis.
- Adjuvant therapy in inflammatory diseases with severe pain in ear, nose or throat (e.g. such as faringotonsillit, otitis media). According to the general principles of treatment, the treatment for cause is essential. Only fever is not an indication.

4.2 Posology and method of administration

Posology:

As a general recommendation, the dose should be adjusted according to the person, and the lowest effective dose should be given for the shortest duration.

Frequency and duration of administration

Adults

The recommended initial daily dose is 100 mg to 150 mg. In mild cases and long-term treatment, 75 to 100 mg per day is usually sufficient.

The treatment applied with tablets during the day to avoid pain at night and morning stiffness can be supported with a suppository (maximum total daily dose should be 150 mg) administered at bedtime.

In primary dysmenorrhea, daily dose should be adjusted individually, and it is usually 50 to 150 mg. Initially, 50 to 100 mg dose should be given and if necessary, the dose should be increased up to maximum 200 mg daily during several menstrual cycle. Treatment should be started when the first symptoms appear and treatment should be continued for several days depending on symptomatology.

Method of Administration:

The suppositories should be inserted well into the rectum. It is recommended to insert the suppositories after passing stools.

Not to be taken by mouth, as per rectal administration only.

Suppositories should not be cut, should be used undividedly.

Children and adolescents

CLODIFEN 100 mg Suppositories is not suitable for children and adolescents.

Additional information on special populations:

Renal/Liver impairment: It should not be used in severe renal and liver and heart failure. (see Section 4.3 and 4.4)

Pediatric population: In children 1 year old and over and adolescents, 0.5 to 2 mg / kg / body weight daily dose should be administered in divided doses into 2 or 3 according to severity of the disease. The daily dose for the treatment of juvenile rheumatoid arthritis can be increased up to maximum 3 mg/kg in divided doses. The highest daily dose should not exceed 150 mg.

Geriatric population: In elderly patients, basic medical principals should be paid attention. Specifically, the lowest effective dose is recommended in weak and elderly patients with low body weight.

4.3. Contraindications

- Hypersensitivity to the active substance, sodium metabisulphite or any of the excipients.
- Active, gastric or intestinal ulcer, bleeding or perforation
- Last trimester of pregnancy (see section 4.6 Pregnancy and lactation)
- Severe hepatic, renal or cardiac failure (see section 4.4 Special warnings and precautions for use)
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contraindicated in patients in whom attacks of asthma, angioedema, urticaria or acute rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs.
- It should not be used in case of proctitis. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in this patients
- Perioperative pain treatment on Coronary artery bypass graft (CABG) surgery

4.4. Special warnings and precautions for use

General

Undesirable effects may be minimised 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 indicated in the elderly on basic medical grounds. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight. As with other nonsteroidal anti-inflammatory drugs including diclofenac, allergic reactions, including anaphylactic/anaphylactoid reactions can also occur without earlier exposure to the drug.

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

The sodium metabisulphite present in solution for injection can also lead to isolated severe hypersensitivity reactions and bronchospasm.

Gastrointestinal effects:

Gastrointestinal bleeding (haematemesis, melaena), 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 GI events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving diclofenac, the drug 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, or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses including diclofenac, and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation.

The elderly have increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage 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 for these patients, and also for patients requiring concomitant use of medicinal products containing low dose acetylsalicylic acid (ASA/aspirin or medicinal products likely to increase gastrointestinal risk.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding).

Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants such as

warfarin, selective serotonin-reuptake inhibitors (SSRIs) or anti-platelet agents such as acetylsalicylic acid.

Close medical surveillance and caution should be exercised in patients with ulcerative colitis, or with Crohn's disease as these conditions may be exacerbated.

Hepatic effects:

Close medical surveillance is required when prescribing CLODIFEN to patients with impairment of hepatic function as their condition may be exacerbated.

As with other 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, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), CLODIFEN should be discontinued.

Hepatitis may occur with diclofenac without prodromal symptoms.

Caution is called for when using diclofenac in patients with hepatic porphyria, since it may trigger an attack.

Renal effects:

As fluid retention and oedema have been reported in association with NSAIDs 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 those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery. Monitoring of renal function is recommended as a precautionary measure when using diclofenac in such cases. Discontinuation therapy is usually followed by recovery to the pre-treatment state.

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 CLODIFEN. Patients appear to be at the 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. CLODIFEN should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

SLE and mixed connective tissue disease:

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

Cardiovascular and cerebrovascular effects:

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, 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 therapy should be re-evaluated periodically.

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy including diclofenac.

Clinical trial and epidemiological data consistently point towards increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (150mg daily) and in long term treatment.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with diclofenac after careful consideration.

Haematological effects:

During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of the blood count is recommended.

Diclofenac may reversibly inhibit platelet aggregation. Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities 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 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.

Like other drugs that inhibit prostaglandin synthetase activity, diclofenac sodium and other NSAIDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of bronchial asthma.

Female fertility:

The use of diclofenac sodium may impair female fertility and is not recommended in women attempting to conceive. In women who may have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of diclofenac sodium should be considered (see section 4.6 Pregnancy and Lactation).

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions include those observed with diclofenac gastro-resistant tablets and/or other pharmaceutical forms of diclofenac.

Lithium: If used concomitantly, CLODIFEN may increase plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

Digoxin: If used concomitantly, CLODIFEN may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

Diuretics and antihypertensive agents: Like other NSAIDs, concomitant use of CLODIFEN with diuretics and antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis.

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 periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity.

Drugs known to cause hyperkalemia: Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored (see section 4.4 Special warnings and precautions for use).

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding (see section 4.4 Special warnings and precautions for use). Although clinical investigations do not appear to indicate that CLODIFEN has an influence on the effect of anticoagulants, there are isolated reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulant concomitantly (see section 4.4 Special warnings and precautions for use). Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other nonsteroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

Other NSAIDs including cyclooxygenase-2 selective inhibitors and corticosteroids: Co-administration of diclofenac with other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration. Avoid concomitant use of two or more NSAIDs (see section 4.4 Special warnings and precautions for use).

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of SSRI's may increase the risk of gastrointestinal bleeding (see section 4.4 Special warnings and precautions for use).

Antidiabetics: Clinical studies have shown that CLODIFEN can be given together with oral antidiabetic agents without influencing their clinical effect. However there have been isolated reports of hypoglycaemic and hyperglycaemic 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: Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased. Cases of serious toxicity have been reported when methotrexate and NSAIDs including diclofenac are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.

Ciclosporin: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. This might be mediated through renal antiprostaglandin effects of both NSAID and calcineurin inhibitor.

Quinolone antibacterials: Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.

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

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.

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

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

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.

4.6 Pregnancy and lactation

Pregnancy and lactation

General Advice:

Pregnancy category: C/D (3rd trimester)

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 or cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1% up to approximately 1.5%.

The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has shown to result in increased pre-and post-implantation loss and embryo-foetal lethality.

In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during organogenetic

period. If CLODIFEN is used by a woman attempting to conceive, or during the 1st 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-hydroamniosis

The mother and the neonate, at the end of the pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses

- inhibition of uterine contractions resulting in delayed or prolonged labour

Consequently, CLODIFEN is contra-indicated during the third trimester of pregnancy.

Lactation

Like other NSAIDs, diclofenac passes into breast milk in small amounts. Therefore, diclofenac should not be administered during breast feeding in order to avoid undesirable effects in the infant (see section 5.2 Pharmacokinetic properties).

Female fertility

As with other NSAIDs, the use of diclofenac may impair female fertility and is not recommended in women attempting to conceive. 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

Patients who experience visual disturbances, dizziness, vertigo, somnolence, central nervous system disturbances, drowsiness or fatigue while taking NSAIDs should refrain from driving or operating machinery.

4.8 Undesirable Effects

Adverse reactions are ranked under the heading of frequency, the most frequent first, using the following convention: very common: (>1/10); common ($\geq 1/100$, <1/10); uncommon (\geq

1/1,000, <1/100); rare (\geq 1/10,000, <1/1000); very rare (<1/10,000); not known: cannot be estimated from available data.

The following undesirable effects include those reported with other short-term or long-term use.

Blood and lymphatic system disorders

Very rare: Thrombocytopenia, leucopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.

Immune system disorders

Rare: Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).

Very rare: Angioneurotic oedema (including face oedema).

Psychiatric disorders

Very rare: Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.

Nervous system disorders

Common: Headache, dizziness.

Rare: Somnolence, tiredness.

Very rare: Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.

Unknown: Confusion, hallucinations, disturbances of sensation, malaise.

Eye disorders

Very rare: Visual disturbance, vision blurred, diplopia.

Unknown: Optic neuritis.

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, hypotension, 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 haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer with or without bleeding or perforation (sometimes fatal particularly in the elderly).

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.

Hepatobiliary disorders

Common: Transaminases increased.

Rare: Hepatitis, jaundice, liver disorder.

Very rare: Fulminant hepatitis, hepatic necrosis, hepatic failure.

Skin and subcutaneous tissue disorders

Common: Rash.

Rare: Urticaria.

Very rare: Bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic 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: Injection site reaction, injection site pain, injection site induration

Rare: Oedema

Reproductive system and breast disorders

Very rare: Impotence

4.9 Overdose

Symptoms

There is no typical clinical picture resulting from diclofenac overdosage. Overdosage can cause symptoms such as vomiting, gastrointestinal haemorrhage, diarrhoea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible.

Therapeutic measures

Management of acute poisoning with NSAIDs, including diclofenac, consists essentially of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

Special measures such as forced diuresis, dialysis, or haemoperfusion are probably unlikely to be helpful in accelerating the elimination of NSAIDs, including diclofenac, because of their high protein-binding rate and extensive metabolism.

5.PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-steroidal Anti-inflammatory and antirheumatic products, non-steroids, acetic acid derivatives and related substances (NSAID)

ATC code: M01AB05

Mechanism of action

CLODIFEN 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 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

In rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac elicit a clinical response characterised 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 rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound oedema.

In clinical trials, significant analgesic effect of diclofenac sodium on not rheumatic, moderate to severe pain has been reported. In addition, clinical studies have showed that diclofenac sodium treats the pain and reduces the extent of bleeding in primary dysmenorrhea.

5.2 Pharmacokinetics properties

Absorption

Suppositories have a more rapid onset, but slower rate of absorption than oral enteric-coated tablets. Cmax is approximately 2/3 of that produced by an equivalent 50 mg enteric-coated tablet oral dose. Tmax occurs within one hour. The unchanged diclofenac plasma AUC values for rectal administration are within the range of values produced by equivalent oral enteric-coated tablet doses. Absorbed amount is related to the dosage linearly.

Since about half the active substance is metabolised during its first passage through the liver

("first pass" effect), the area under the concentration curve (AUC) following oral or rectal administration is about half as large as it is following a parenteral dose of equal size. In repeated dose, pharmacokinetic behavior does not change after administration. Accumulation does not occur if recommended dose intervals are administered.

Following administration of equivalent doses (mg/kg body weight), plasma concentrations obtained in children is similar to that achieved in adults.

Distribution

The active substance is 99.7% protein bound, mainly to serum albumin (99.4%). Volume of distribution is 0.12 to 0.17 L/kg.

Diclofenac enters the synovial fluid, where maximum concentrations are measured 2-4 hours after the peak plasma values have been attained. The apparent half-life for elimination from the synovial fluid is 3-6 hours. Two 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.

Biotransformation / Metabolism

Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites (3'-hydroxy-, 4'- hydroxy -,5- hydroxy -,4', 5-dihydroxy and 3'- hydroxy -4'methoxy-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 $263 \pm 56 \text{ mL/min}$ (mean value $\pm \text{SD}$). 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. Plasma half-life of a metabolite (3'-hydroxy-4'-methoxy-diclofenac) is longer. However, this metabolite is almost ineffective. 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 faeces.

Characteristics in patients

No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed.

Patients with 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 less than 10 mL/min, the calculated steady-state plasma levels of the hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.

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

5.3 Preclinical 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. Except for minimal fetal effects at maternally toxic doses the prenatal, perinatal, and postnatal development of the offspring was not affected.

Teratogenic effect has not been detected on rats, mice and rabbits. Mutagenic effects have not been reported in various vitro and in vivo experiments and carcinogenic potential has not been detected in long-term studies performed on rats and mice.

6.PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Hard Fat Witepsol (S55)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 30°C.

Keep out of the reach and sight of children.

6.5 Nature and contents

Cardbox contains 2 PVC/PE foil blisters including 5 suppositories in each.

6.6 Special precautionsfor disposal and other handling

Any unused product or waste material should be destroyed according to "Medical Material Control Regulation" and "Packaging and Packaging Waste Control Regulation".

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT