SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE PRODUCT

LOFNAC-100

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each suppository contains 100 mg diclofenac sodium (BP).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICA L FORM

Suppositories - White to off white bullet shaped suppositories

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults and Elderly:

Relief of all grades of pain and inflammation in a wide range of conditions, including:

(i) arthritic conditions: rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout,

(ii) Acute musculo-skeletal disorders such as periarthritis (for ex ample frozen shoulder), tendinitis, tenosynovitis, bursitis,

(iii) other painful conditions resulting from trauma, including fracture, l ow back pain, sprains, strains, dislocations, orthopaedic, dental and other minor surgery.

4.2 Posology and Method of Administration

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4 Special warnings and precautions for use).

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

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

Adults: 75-150mg daily, in divided doses.

The recommended maximum daily dose of LOFNAC-100 is 150 mg. This may be administered using a combination of dosage forms, e.g. tablets and suppositories. Where necessary, therapy may be combined with 25 mg or 50mg tablets or suppositories up to the maximum dose of 150 mg per day.

Elderly: Although the pharmacokinetics of LOFNAC-100 are not impaired to any clinically relevant extent in elderly patients, nonsteroidal 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 bod y weight (see also Precautions) and the patient should be monitored for GI bleeding during NSAID therapy.

4.3 Contraindications

• Hypersensitivity to the active substance or any of the excipients.

• Patients with active, or a history of, gastrointestinal ulcers, bleeding or perforation (two or more distinct episodes of proven ulceration or bleeding).

• Patients who have previously shown hyper-sensitivity reactions (e.g. asthma, angioedema, urticaria or acute rhinitis) to ibuprofen, aspirin or other nonsteroidal anti-inflammatory drugs.

• Severe hepatic, renal and heart failure (see section 4.4 Special warnings and precautions for use).

• During the last trimester of pregnancy (see section 4.6 Pregnancy and lactation).

• History of gastrointestinal bleeding or perforation, relating to previous NSAID therapy.

4.4 Special Warnings and Precautions for Use

General

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2 and GI and cardiovascular risks below). 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 (see section 4.5).

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 (see section 4.2).

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug (see section 4.8).

Like other NSAIDs, suppositories ma y mask the signs and symptoms of infection due to its pharmacodynamics properties.

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 gastrointestinal events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving suppositories, 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 (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see section 4.8).

The risk of GI bleeding, is higher with increasing NSAID doses, and in patients with a history of ulcer, particularly if complicated with hemorrhage or perforation.

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which ma y be fatal (see section 4.2).

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 maintain 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 other medicinal products likely to increase gastrointestinal risk (See section 4.5).

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

Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, such as warfarin, anti-platelet agents such as acetylsalicylic acid or selective serotonin-reuptake inhibitors (see section 4.5).

Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be ex acerbated (see section 4.8).

Hepatic effects:

Close medical surveillance is required when prescribing Diclofenac to patients with impaired 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, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash), Diclofenac should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms.

Caution is called for when using Diclofenac in patients with hepatic porph yria, since it may trigger an attack.

Renal effects

As fluid retention and oedema have been reported in association with NSAID therapy, including diclofenac, particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in those patients with substantial extracellular volume depletion 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. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, those being treated with diuretics or recovering from major surgery.

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, (see section 4.8). 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. Suppositories 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 (see section 4.8).

Cardiovascular and cerebrovascular effects

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 ma y 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 (150 mg 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:

Use of suppositories is recommended only for short term treatment. During prolonged treatment with Diclofenac, as with other NSAIDs, monitoring of the blood count is recommended. Diclofenac may reversibly inhibit platelet aggregation (see section 4.5). Patients with defects of hemostasis, bleeding diathesis or hematological abnormalities should be carefully monitored.

Pre-existing asthma

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal pol yps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract

(especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma ex acerbations (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 NSA IDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of bronchial asthma.

Female fertility:

The use of suppositories ma y 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 suppositories should be considered (see section 4.6).

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, diclofenac ma y raise plasma concentrations of lithium.

Monitoring of the serum lithium level is recommended.

Digoxin: If used concomitantly, diclofenac ma y raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

Diuretics and antihypertensive agents:

Like other NSAIDS, concomitant use of Suppositories 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 and 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 drugs ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently (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 diclofenac affects the action of anticoagulants here are reports of an increased risk of hemorrhage in patients receiving diclofenac and anticoagulants concomitantly (see section 4.4). Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required.

As with other non-steroidal 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 and other systemic NSA IDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration. Avoid concomitant use of two or more NSAIDs (see section 4.4).

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

Antidiabetics: Clinical studies have shown that suppositories 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:

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 or after 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 antiprostagladin effects of both NSAID and calcineurin inhibitor.

Quinolone antibacterial: 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 CY P2C9 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 concentration and exposure to diclofenac due to inhibition of diclofenac metabolism..

4.6 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 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 Diclofenac 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 ex pose the foetus to:

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)
- Renal dysfunction, which ma y 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 ma y occur even at very low doses
- inhibition of uterine contractions resulting in delayed or prolonged labour

Consequently, Diclofenac is contra-indicated during the third trimester of pregnancy. Lactation Like other NSA IDs, 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).

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 ma y have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of diclofenac should be considered. (See also section 4.4).

4.7 Effects on ability to drive and use machines

Patients who experience dizziness, drowsiness, fatigue or visual disturbances, while taking NSAIDS should refrain from driving or operating machinery.

4.8 Undesirable effects

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: 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 either short-term or long-term use.

Table 1:

Blood and lymphatic system disorders	
Very rare	Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), Agranulocytosis.
Immune system disorders	
Rare Very rare	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock). Angioneurotic oedema (including
Psychiatric disorders	
Very rare	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders	
Common Rare Very rare Unknown	Headache, dizziness. Somnolence, tiredness Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic Meningitis, taste disturbance cerebrovascular accident. Hallucination, confusion, malaise, disturbances sensation
Eye disorders	
Very rare Unknown	Visual disturbance, vision blurred, diplopia. Optic Neuritis
Ear and labyrinth disorders	
Common Very rare	Vertigo. Tinnitus, hearing impaired.
Cardiac disorders	
Uncommon	Myocardial infarction, cardiac failure, palpitations, chest pain
Vascular disorders	
Very rare	Hypertension, hypotension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Rare Very rare	Asthma (including dyspnoea). 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.
Unknown	Ischaemic colitis.
Hepatobiliary disorders	
Common	Transaminases increased.
Rare	Hepatitis, jaundice, liver disorder.
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,
Renal and urinary disorders	
Very rare	Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.
Reproductive system and breast disorders	
Very rare	Impotence
General disorders and administration site conditions	
Rare	Application site irritation, oedema

Clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events (for ex ample myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (150mg daily) and in long term treatment (see section 4.3 and 4.4 for Contraindications and Special warnings and special precautions for use).

4.9 Overdose

Symptom:

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, ex citation, coma, drowsiness, tinnitus, fainting, occasionally and convulsions. In rare cases of significant poisoning acute renal failure and liver damage are possible.

Therapeutic measures:

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults gastric lavage should be considered within one hour of ingestion of potentially toxic amounts. Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures ma y be indicated by the patients clinical condition.

5. PHARMACOLOGI CAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group

Nonsteroidal anti-inflammatory drugs (NSAIDs).

Mechanism of action

LOFNAC-100 is a nonsteroidal agent with marked analgesic/anti- inflammatory properties. It is an inhibitor of prostaglandin synthetase, (cyclo-oxygenase).

Diclofenac sodium in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings.

5.2 Pharmacokinetic properties

Absorption

Absorption is rapid; although the rate of absorption is slower than from enteric-coated tablets administered orally. After the rectal administration of 50mg diclofenac, peak plasma concentrations are attained on average within 1 hour, but maximum concentrations per dose unit are about two thirds of those reached after administration of enteric-coated tablets (1.95 ± 0.8µg/ml (1.9µg/ml ≡ 5.9µmol/l)). Bioavailability

Pharmacokinetic behavior does not change on repeated administration. Accumulation does not occur, provided the recommended dosage intervals are observed.

Distribution

The active substance is 99.7% protein bound, mainly to albumin (99.4%).

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 the y are in the plasma and remain higher for up to 1 2 hours.

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

Elimination

The total systemic clearance of diclofenac in plasma is 263 ± 56 m L/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.

Characteristics in patients

No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed, other than the finding that in five elderly patients, a 15 minute IV infusion resulted in 50% higher plasma concentrations than expected with young healthy subjects.

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 m L/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

None stated

6. PHARMACEUTICA L PROPERTIES

6.1 List of excipients

PEG 1500, PEG 6000methyl paraben, propyl paraben, Butylated hydroxyl toluene, titanium dioxide

6.2 Incompatibilities

None Known

6.3 Shelf life

Three years

6.4 Special precautions for storage

Store protected from light at temperature not exceeding 30°C.

6.5 Nature and contents of container

2 x 5 Suppositories packed in PVC/PE foil in carton along with pack insert

6.6 Special precautions for disposal and other handling: For rectal use only

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

Marketing Authorisation Holder

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8.MARKETING AUTHORISATION NUMBER : ---

9. DATE OF FIRST AUTHORISATION OR RENEWAL : ------

10. DATE OF REVISION OF THE TEXT : -----