Summary of Product Characteristics

LOFNAC-50
Diclofenac Sodium Suppositories

1. NAME OF THE PRODUCT
LOFNAC-50

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
The active substance is Benzeneacetic acid, 2-[(2, 6-dichlorophenyl) amino] - monosodium salt. Sodium [*o*-(2, 6-dichloroanilino) phenyl] acetate.
Each suppository contains 50mg diclofenac sodium (BP).
White to off white opaque bullet shaped suppositories
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
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 example frozen shoulder), tendinitis, tenosynovitis, bursitis,
(iii) other painful conditions resulting from trauma, including fracture, low back pain, sprains, strains, dislocations, orthopaedic, dental and other minor surgery.
LOFNAC-50 suppository is not indicated for use in children.

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-50 is 150 mg. This may be administered using a combination of dosage forms, e.g. tablets and suppositories.

Elderly: Although the pharmacokinetics of LOFNAC-50 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 body 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

Warnings

In all patients:

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

The use of LOFNAC-50 with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5 Interactions with other medicaments and other forms of interaction).

Elderly:

The elderly have increased frequency of adverse reactions to NSAIDs especially gastro intestinal bleeding and perforation which may be fatal (see section 4.2 Posology and method of administration).

Gastrointestinal: As with all NSAIDs, including diclofenac close medical surveillance is imperative in patients with symptoms indicative of gastrointestinal disorders, with a history suggestive of gastric or intestinal ulceration, with ulcerative colitis, or with Crohn's disease as these conditions may be exacerbated (see section 4.8 Undesirable effects).

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

Gastrointestinal bleeding or ulceration/perforation: haematemesis melaena ulceration or perforation which can be fatal has been reported with all NSAIDs, including diclofenac. They can occur at any time during treatment, with or without warning symptoms or a previous history

of serious GI events. In the rare instances when gastrointestinal bleeding or ulceration occurs in patients receiving LOFNAC-50, the drug should be withdrawn.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, including diclofenac, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3 Contraindications), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, other drugs likely to increase gastrointestinal risk (see below and section 4.5 Interactions with other medicaments and other forms of interaction).

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors (SSRIs) or anti-platelet agents such as aspirin (see section 4.5 Interaction with other medicaments and other forms of interaction).

Hepatic: Close medical surveillance is also imperative in patients suffering from impairment of hepatic function.

Hypersensitivity reactions: As with other nonsteroidal anti-inflammatory drugs, including diclofenac allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug (see section 4.8 Undesirable effects).

Like other NSAIDs, LOFNAC-50 may mask the signs and symptoms of infection due to its pharmacodynamic properties.

Precautions

Renal: Patients with renal, cardiac or hepatic impairment and the elderly should be kept under surveillance, since the use of NSAIDs, including diclofenac may result in deterioration of renal function. The lowest effective dose should be used and renal function monitored.

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. Effects on renal function are usually reversible on withdrawal of LOFNAC-50.

Hepatic: If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), LOFNAC-50 should be discontinued. Hepatitis may occur with diclofenac without prodromal symptoms.

Use of LOFNAC-50 in patients with hepatic porphyria may trigger an attack.

Haematological: LOFNAC-50 may reversibly inhibit platelet aggregation (see anticoagulants in section 4.5 Interaction with other medicaments and other forms of interactions). Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.

Long term treatment: All patients who are receiving nonsteroidal anti-inflammatory agents should be monitored as a precautionary measure e.g. renal function, hepatic function (elevation of liver enzymes may occur) and blood counts. This is particularly important in the elderly.

Respiratory disorders:
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.
Cardiovascular and cerebrovascular effects:-
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 suggest that use of diclofenac, particularly at high dose (150mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).
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. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking).
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 Undesirable effects).
Dermatological: 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 LOFNAC-50 (see section 4.8 Undesirable effects). 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. LOFNAC-50 should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.
Female fertility:
The use of LOFNAC-50 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 LOFNAC-50 should be considered.

4.5 Interaction with other medicinal products and other forms of interaction
Lithium and digoxin: LOFNAC-50 may increase plasma concentrations of lithium and digoxin.
Anticoagulants: Although clinical investigations do not appear to indicate that LOFNAC-50 has an influence on the effect of anticoagulants, there are isolated reports of an increased risk of haemorrhage with the combined use of diclofenac and anticoagulant therapy (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.

Antidiabetic agents: Clinical studies have shown that LOFNAC-50 can be given together with oral antidiabetic agents without influencing their clinical effect. However there have been isolated reports of hypoglycaemic and hyperglycaemic effects which have required adjustment to the dosage of hypoglycaemic agents.

Methotrexate: 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.

Quinolone antimicrobials: 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.

Potent CYP2C9 inhibitors: Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as sulfinpyrazone and voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

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

Other NSAIDs including cyclooxygenase-2 selective inhibitors and corticosteroids: Co-administration of LOFNAC-50 with aspirin 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).

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of systemic NSAIDs, including diclofenac may cause increased risk of gastrointestinal bleeding (see section 4.4 Special warnings and precautions for use).

Diuretics: Like other NSAIDs, LOFNAC-50 may inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, which should therefore be monitored frequently.

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.

Antihypertensives: Concomitant use of NSAIDs with antihypertensive drugs (i.e. beta-blockers, angiotensin converting enzyme (ACE) inhibitors, diuretics) may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis.

Ciclosporin and Tacrolimus: Cases of nephrotoxicity have been reported in patients receiving concomitant ciclosporin and NSAIDs, including diclofenac sodium. 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.

4.6 Pregnancy and Lactation

Pregnancy

Congenital abnormalities have been reported in association with the administration of NSAIDs in man, however, these are low in frequency and do not appear to follow any discernible pattern.

In view of the known effects of NSAIDs, including diclofenac on the foetal cardiovascular system (e.g. a premature closure of the ductus arteriosus) and in causing uterine inertia, use in the last trimester of pregnancy is contraindicated. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child (see section 4.3 Contraindications). NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit outweighs the potential risk to foetus. The lowest effective dose should be used and duration kept as short as possible.

Lactation

Like other NSAIDs, diclofenac passes into breast milk in small amounts and therefore NSAIDs should if possible be avoided when breastfeeding.

See section 4.4 Special warnings and precautions for use, regarding female fertility.

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 events

If serious side-effects occur, LOFNAC-50 should be withdrawn.

Frequency estimate: frequent:>10 %, occasional:>1 - 10 %, rare:>0.001 - 1 %, isolated cases: <0.001 %.

Gastrointestinal tract

Occasional: Epigastric pain, other gastrointestinal disorders (e.g. nausea, vomiting, diarrhoea, abdominal cramps, dyspepsia, flatulence, anorexia).

Rare: Gastritis, gastrointestinal bleeding (haematemesis, melaena, and bloody diarrhoea), gastrointestinal ulcers with or without bleeding or perforation (sometimes fatal, particularly in the elderly) may occur (see section 4.4 Special warnings and precautions for use).

In isolated cases: Aphthous stomatitis, glossitis, oesophageal lesions, lower gut disorders (e.g. non-specific haemorrhagic colitis and exacerbations of ulcerative colitis or Crohn's proctocolitis, colonic damage and stricture formation), pancreatitis, constipation.

Suppositories only:

Occasional: Local reactions (e.g. itching, burning and increased bowel movement). In isolated cases: Exacerbation of haemorrhoids.

Central Nervous System disorders:

Occasional: Headache, dizziness, or vertigo.

Rare: Drowsiness, tiredness hypotension.

In isolated cases: Disturbances of sensation, paraesthesia, memory disturbance, disorientation, insomnia, irritability, convulsions, depression, confusion, hallucinations, malaise, anxiety, nightmares, tremor, psychotic reactions, aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus and mixed tissue disease), with symptoms such as fever, stiff neck, headache, nausea and vomiting.

Special senses:

Isolated cases: Disturbances of vision (blurred vision, optic neuritis, diplopia), impaired hearing, tinnitus, taste disturbances.

Skin:

Occasional: Rashes or skin eruptions.

Rare: Urticaria.

In isolated cases: Bullous eruptions, eczema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome, (acute toxic epidermolysis), erythroderma (exfoliative dermatitis), loss of hair, photosensitivity reactions, purpura including allergic purpura.

Kidney:

Rare: Oedema.

In isolated cases: Acute renal insufficiency, urinary abnormalities (e.g. haematuria, proteinuria), interstitial nephritis, nephrotic syndrome, papillary necrosis.

Liver:

Occasional: Elevation of serum aminotransferase enzymes (ALT, AST).

Rare: Liver function disorders including hepatitis (in isolated cases fulminant) with or without jaundice.

Blood:

In isolated cases: Thrombocytopenia, leucopenia, agranulocytosis, haemolytic anaemia, aplastic anaemia.

Vascular:

Isolated cases: Vasculitus.

Respiratory:

Isolated cases: Pneumonitis.

Cardiovascular system:

Isolated cases: Palpitations, chest pain, hypertension, congestive heart failure.

Other organ systems:

Isolated cases: Impotence.

Hypersensitivity:

Hypersensitivity reactions have been reported following treatment with NSAIDs. These consist of (a) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising of asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura angiodema and, more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Clinical trial and epidemiological data suggest that use of diclofenac, particularly at high doses (150mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4 Special warnings and special precautions for use).

4.9 Overdose

Symptoms:

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, tinnitus, fainting, occasional 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 may be indicated by the patient's clinical condition.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Nonsteroidal anti-inflammatory drugs (NSAIDs).

Mechanism of action

LOFNAC-50 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 administration of 50mg suppositories, 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 behaviour 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 they are in the plasma and remain higher for up to 12 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 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.

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 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

None stated

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

PEG, methyl paraben, propyl paraben, BHT, titanium dioxide

6.2 Incompatibilities

None Known

6.3 Shelf life
Three Years

6.4 Special precautions for storage
Store in a dry place, below 30ºC.
Protect from light
Keep out of reach and sight of children.

6.5 Nature and contents of container
The suppositories are white to off white opaque bullet shaped suppository.
2 x 5 Suppositories packed in PVC/PE foil in carton along with pack inserts

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

7. MARKETING AUTHORISATION HOLDER
Bliss GVS Pharma Ltd., Saki Vihar Road, Andheri (East), Mumbai - 400 072.

8. DATE OF REVISION OF THE TEXT
