SUMMARY OF PRODUCT CHARACTERISTICS

LOFNAC 75/100

(Diclofenac Sodium Prolonged Release Tablet BP 75mg / 100mg)

1. NAME OF THE PRODUCT

LOFNAC 75/100

(Diclofenac Sodium Prolonged Release Tablet BP 75mg / 100mg)

2. Quantitative and Qualitative Composition:

Each prolonged release tablet contains:

Diclofenac Sodium BP (75 mg/100 mg)

Excipients (- QS)

For full list of excipients, refer section 6.1

3. Pharmaceutical Forms:

Oral Tablet

4. Therapeutic Indication:

Carefully consider the potential benefits and risks of **LOFNAC 75/100** (**Diclofenac Sodium Prolonged Release Tablet BP 75mg / 100mg**) and other treatment options before deciding to use LOFNAC 75/100. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.

LOFNAC 75/100 is indicated:

- For relief of the signs and symptoms of osteoarthritis
- For relief of the signs and symptoms of rheumatoid arthritis
- For acute or long-term use in the relief of signs and symptoms of ankylosing spondylitis

4.1 Posology and Method of Administration:

Posology

Adults: One tablet once or twice daily.

The recommended maximum daily dose of Diclofenac Sodium is 150 mg

Childrens:

Diclofenac Sodium 75 & 100 mg prolonged release tablets are not suitable for childrens.

Method of administration

LOFNAC – 75 /100 tablets is for oral use only.

4.2 Contraindication:

- **LOFNAC 75/100 (Diclofenac Sodium Prolonged Release Tablet BP 75mg / 100mg)** is contraindicated in patients with known hypersensitivity to diclofenac.
- Active, gastric or intestinal ulcer, bleeding or perforation.
- History of gastrointestinal bleeding or perforation, relating to previous NSAIDs therapy.
- Active, or history of recurrent peptic ulcer / hemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Last trimester of pregnancy
- Hepatic failure
- Renal failure
- Established congestive heart failure (NYHA-11-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- 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.
- **LOFNAC 75/100 (Diclofenac Sodium Prolonged Release Tablet BP 75mg / 100mg)** should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients
- **LOFNAC 75/100 (Diclofenac Sodium Prolonged Release Tablet BP 75mg / 100mg)** is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.

4.3 Special Warning and Special Precaution for Use:

Cardiovascular Effects

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see WARNINGS, GI Effects).

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see CONTRAINDICATIONS).

Hypertension

NSAIDs can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including **LOFNAC 75/100 (Diclofenac Sodium Prolonged Release Tablet BP 75mg / 100mg)**, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs. LOFNAC 75/100 should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal (GI) Effects: Risk of GI Ulceration, Bleeding, and Perforation

NSAIDs, including LOFNAC 75/100, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects

Caution should be used when initiating treatment with **LOFNAC 75/100** in patients with considerable dehydration.

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a

nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced Renal Disease

No information is available from controlled clinical studies regarding the use of **LOFNAC 75/100** in patients with advanced renal disease. Therefore, treatment with **LOFNAC 75/100** is not recommended in these patients with advanced renal disease. If **LOFNAC 75/100** therapy must be initiated, close monitoring of the patient's renal function is advisable.

Hepatic Effects

Elevations of one or more liver tests may occur during therapy with **LOFNAC 75/100.** These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations (i.e., less than 3 times the ULN [ULN = the upper limit of the normal range]) or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients. Of the markers of hepatic function, ALT (SGPT) is recommended for the monitoring of liver injury.

In clinical trials, meaningful elevations (i.e., more than 3 times the ULN) of AST (GOT) (ALT was not measured in all studies) occurred in about 2% of approximately 5,700 patients at some time during diclofenac treatment. In a large, open-label, controlled trial of 3,700 patients treated for 2-6 months, patients were monitored first at 8 weeks and 1,200 patients were monitored again at 24 weeks. Meaningful elevations of ALT and/or AST occurred in about 4% of patients and included marked elevations (i.e., more than 8 times the ULN) in about 1% of the 3,700 patients. In that open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3-8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Elevations in transaminases were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis.

Almost all meaningful elevations in transaminases were detected before patients became symptomatic. Abnormal tests occurred during the first 2 months of therapy with diclofenac in 42 of the 51 patients in all trials who developed marked transaminase elevations.

In postmarketing reports, cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases, the first 2 months of therapy, but can occur at any time during treatment with diclofenac. Postmarketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation.

Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. Based on clinical trial data and postmarketing experiences, transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac. However, severe hepatic reactions can occur at any time during treatment with diclofenac.

If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, abdominal pain, diarrhea, dark urine, etc.), **LOFNAC 75/100** should be discontinued immediately.

To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms), and the appropriate action patients should take if these signs and symptoms appear.

To minimize the potential risk for an adverse liver related event in patients treated with LOFNAC 75/100, the lowest effective dose should be used for the shortest duration possible. Caution should be exercised in prescribing LOFNAC 75/100 with concomitant drugs that are known to be potentially hepatotoxic (e.g., antibiotics, anti-epileptics).

Anaphylactic Reactions

As with other NSAIDs, anaphylactic reactions may occur both in patients with the aspirin triad and in patients without known sensitivity to NSAIDs or known prior exposure to LOFNAC 75/100. LOFNAC 75/100 should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. (See CONTRAINDICATIONS and PRECAUTIONS, Preexisting Asthma.) Anaphylaxis-type reactions have been reported with NSAID products, including with diclofenac

products, such as LOFNAC 75/100. Emergency help should be sought in cases where an anaphylactic reaction occurs.

Skin Reactions

NSAIDs, including LOFNAC 75/100, can cause serious skin adverse events such as exfoliative dermatitis, Stevens - Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy

In late pregnancy, as with other NSAIDs, LOFNAC 75/100 should be avoided because it may cause premature closure of the ductus arteriosus.

4.4 Interaction with other medicaments and other forms of interaction:

Aspirin: When LOFNAC 75/100 is administered with aspirin, its protein binding is reduced. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of diclofenac and aspirin is not generally recommended because of the potential of increased adverse effects.

Methotrexate: NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Cyclosporine: LOFNAC 75/100, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Therefore, concomitant therapy with LOFNAC 75/100 may increase cyclosporine's nephrotoxicity. Caution should be used when LOFNAC 75/100 is administered concomitantly with cyclosporine.

ACE Inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.

Furosemide: Clinical studies, as well as post marketing observations, have shown that LOFNAC 75/100 can reduce the natriuretic effect of furosemide and thiazides in some patients.

This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see WARNINGS, Renal Effects), as well as to assure diuretic efficacy.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

CYP2C9 Inhibitors or Inducers: Diclofenac is metabolized by cytochrome P450 enzymes, predominantly by CYP2C9. Co-administration of diclofenac with CYP2C9 inhibitors (e.g. voriconazole) may enhance the exposure and toxicity of diclofenac whereas co-administration with CYP2C9 inducers (e.g. rifampin) may lead to compromised efficacy of diclofenac. Use caution when dosing diclofenac with CYP2C9 inhibitors or inducers; a dosage adjustment may be warranted (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug Interactions).

4.5 Pregnancy and Lactation:

Pregnancy:

Inhibition of Nonteratogenic Effects:

Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Labor and Delivery

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of LOFNAC 75/100 on labor and delivery in pregnant women are unknown.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from

LOFNAC 75/100, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

As with any NSAIDs, caution should be exercised in treating the elderly (65 years and older).

4.6 Effects on ability to drive and use machines

Not known.

4.7 Undesirable Effects

In patients taking **LOFNAC 75/100 (Diclofenac Sodium Prolonged Release Tablet BP 75mg / 100mg)** or other NSAIDs, the most frequently reported adverse experiences occurring in approximately 1%-10% of patients are:

Gastrointestinal experiences including: abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, GI ulcers (gastric/duodenal) and vomiting.

Abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes and tinnitus.

Additional adverse experiences reported occasionally include:

Table 2. Diclofenac Sodium Adverse Drug Reactions

System Organ Class	**Adverse drug reactions**
Body as a Whole:	fever, infection, sepsis
Cardiovascular System:	congestive heart failure, hypertension, tachycardia, syncope
Digestive System:	dry mouth, esophagitis, gastric/peptic ulcers, gastritis, gastrointestinal bleeding, glossitis, hematemesis, hepatitis, jaundice
Hemic and Lymphatic System:	ecchymosis, eosinophilia, leukopenia, melena, purpura, rectal bleeding, stomatitis, thrombocytopenia
Metabolic and Nutritional:	weight changes

Nervous System:	anxiety, asthenia, confusion, depression, dream abnormalities, drowsiness, insomnia, malaise, nervousness, paresthesia, somnolence, tremors, vertigo
Respiratory System:	asthma, dyspnea
Skin and Appendages:	alopecia, photosensitivity, sweating increased
Special Senses:	blurred vision
Urogenital System:	cystitis, dysuria, hematuria, interstitial nephritis, oliguria/polyuria, proteinuria, renal failure
Rare	
Body as a Whole:	anaphylactic reactions, appetite changes, death
Cardiovascular System:	Arrhythmia, hypotension, myocardial infarction, palpitations, vasculitis.
Digestive System:	Colitis, eructation, fulminant hepatitis with and without jaundice, liver failure, liver necrosis, pancreatitis.
Hemic and Lymphatic System:	agranulocytosis, hemolytic anemia, aplastic anemia, lymphadenopathy, pancytopenia
Metabolic and Nutritional:	hyperglycemia
Nervous System:	convulsions, coma, hallucinations, meningitis
Respiratory System:	respiratory depression, pneumonia
Skin and Appendages:	angioedema, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, urticaria
Special Senses:	conjunctivitis, hearing impairment

4.8 Overdose:

Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed by symptomatic and supportive care following a NSAID overdose. There are no specific antidotes. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion

with symptoms or following a large overdose (5 to 10 times the usual dose). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

Therapeutic measures:

Management of acute poisoning with NSAIDs, including diclofenac, essentially consists of supportive measures and symptomatic treatment.

5. Pharmacological Properties:

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Non-steroidal anti-inflammatory group.

ATC code: M01AB05

Mechanism of action

Diclofenac sodium is a non-steroidal agent with marked analgesic/anti-inflammatory properties. It is an inhibitor prostaglandin synthetase, (cyclo-oxygenase).

5.2 Pharmacokinetic properties

Absorption

Diclofenac is 100% absorbed after oral administration compared to IV administration as measured by urine recovery. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available (see Table 1). Food has no significant effect on the extent of diclofenac absorption. However, there is usually a delay in the onset of absorption of 1 to 4.5 hours and a reduction in peak plasma levels of < 20%.

Distribution

The apparent volume of distribution (V/F) of diclofenac sodium is 1.4 L/kg.

Diclofenac is more than 99% bound to human serum proteins, primarily to albumin. Serum protein binding is constant over the concentration range (0.15-105 μg/mL) achieved with recommended doses.

Diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial

fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.

Metabolism.

Five diclofenac metabolites have been identified in human plasma and urine. The metabolites include 4'-hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3'hydroxy-4'-methoxy-diclofenac. The major diclofenac metabolite, 4'-hydroxy-diclofenac, has very weak pharmacologic activity. The formation of 4'-hydroxy- diclofenac is primarily mediated by CPY2C9. Both diclofenac and its oxidative metabolites undergo glucuronidation or sulfation followed by biliary excretion. Acylglucuronidation mediated by UGT2B7 and oxidation mediated by CPY2C8 may also play a role in diclofenac metabolism. CYP3A4 is responsible for the formation of minor metabolites, 5-hydroxy- and 3'-hydroxy-diclofenac. In patients with renal dysfunction, peak concentrations of metabolites 4'-hydroxy- and 5-hydroxy-diclofenac were approximately 50% and 4% of the parent compound after single oral dosing compared to 27% and 1% in normal healthy subjects.

Excretion

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Little or no free unchanged diclofenac is excreted in the urine. Approximately 65% of the dose is excreted in the urine and approximately 35% in the bile as conjugates of unchanged diclofenac plus metabolites. Because renal elimination is not a significant pathway of elimination for unchanged diclofenac, dosing adjustment in patients with mild to moderate renal dysfunction is not necessary. The terminal half-life of unchanged diclofenac is approximately 2 hours.

Special Populations

Pediatric: The pharmacokinetics of Voltaren has not been investigated in pediatric patients.

Race: Pharmacokinetic differences due to race have not been identified.

Hepatic Insufficiency: Hepatic metabolism accounts for almost 100% of Voltaren elimination, so patients with hepatic disease may require reduced doses of Voltaren compared to patients with normal hepatic function.

Renal Insufficiency: Diclofenac pharmacokinetics has been investigated in subjects with renal insufficiency. No differences in the pharmacokinetics of diclofenac have been detected in studies of patients with renal impairment. In patients with renal impairment (inulin clearance 60-90, 30-

60, and <30 mL/min; N=6 in each group), AUC values and elimination rate were comparable to those in healthy subjects.

5.3 Preclinical Safety Data:

Not Applicable.

6. Pharmaceutical Particulars:

6.1 List of Excipients: Sucrose, Povidone K 30, Cetyl Alcohol, Colloidal Silicon Dioxide, Magnesium Stearate, Opadry Pink 13A540005 and Purified Water.

6.2 Incompatibilities: Not applicable

6.3 Shelf Life: 36 Month from month of manufacture.

6.4 Special Precaution for Storage:

Store below 30°C and protect from moisture.

6.5 Nature and contents of container:

Finished product is packed in blister, such blister of 1 x 10 tablets are packed in monocarton along with pack insert and such 20 monocarton are packed in an outer carton.

6.6 Special precautions for disposal and other handling:

Keep out of reach of children.

7. Marketing Authorization:

BLISS GVS PHARMA LTD

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