SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product: Brand Name:

Lysoflam Tablets
(Paracetamol, Diclofenac Potassium and Serratiopeptidase Tablets)

2. Qualitative and Quantitative composition

Each film coated tablet contains:
Paracetamol BP……..……..……500 mg
Diclofenac Potassium BP …….....50 mg
Serratiopeptidase (Enteric Coated) …….....15 mg
(30000 units Serratiopeptidase)
Colour: Tartrazine

Name of Ingredient	Specification	Quantity/ tablet (in mg)	Function
Paracetamol	BP	500	API
Diclofenac Potassium	BP	50	API
Serratiopeptidase (Enteric Coated) (30% Overages)	In-House	19.50	API
Micro Crystalline Cellulose	BP	76.50	Diluent
Starch	BP	8.10	Diluent
Colour Tartrazine	In-House	0.20	Colouring agent
Methyl Paraben	BP	1.00	Preservative
Propyl Paraben	BP	0.20	Preservative
Starch (For Paste)	BP	30.00	Binder
Starch (For Lubricant)	BP	14.50	Lubricant
Magnesium Stearate	BP	22.50	Lubricant
Talcum Powder	BP	15.00	Glidant
Sodium Starch Glycollate	BP	12.50	Disintegrant
Purified Water	BP	q.s.	Vehicle
Opadry II (85G52193) Yellow	In-House	15.00	Coating agent
Purified Water	BP	q.s.	Vehicle

USP – United State Pharmacopoeia
BP -British Pharmacopoeia
IH – In - House

3. Pharmaceutical Form

Solid Dosage form (Film coated tablet).

Description : Orange yellow colour clear liquid having sweet taste and pleasant flavour.

4. Clinical particulars

4.1 Therapeutic Indications

Acute painful & inflammatory conditions.

4.2 Posology and Method of Administration

Adult & Children (12 years & above) : One tablet twice daily.

Method of administration

Oral Tablets.

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
- During the last trimester of pregnancy.
- History of gastrointestinal bleeding or perforation, relating to previous NSAID therapy.

4.4 Special Warnings and Precautions for Use

In all patients: Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control.

symptoms.

The use of Lysoflam with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

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

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 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 Lysoflam, 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, 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 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

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

4.5 Interaction with other medicinal products and other forms of interaction:

The risk of Paracetamol toxicity may be increased in patients receiving other potentially heatotoxic drugs or drugs that induce hepatic microsomal enzymes.

Coadministration of Paracetamol with rifampicin, isoniazid, chloramphenicol, antiepileptic drugs and antiviral drugs is to be avoided. Metoclopromide may increase the absorption of Paracetamol whereas excretion and plasma concentration may be altered when coadministered with probenecid.

Cholestyramine also reduces the absorption of Paracetamol.

Aspirin

Diclofenac Potassium when 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

Diclofenac Potassium, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Therefore, concomitant therapy with Diclofenac Potassium tablets may increase cyclosporine's nephrotoxicity. Caution should be used when Diclofenac Potassium 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 Diclofenac Potassium 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, 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

Serratiopeptidase: With anticoagulative agents, it may increase anticoagulative effect and therefore LYSOFLAM must not be used in such patients.

4.6 Pregnancy and Lactation

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women.

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

The effects of Lysoflam 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 Lysoflam, 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.

4.7 Effects on Ability to Drive and Use Machine

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines.

4.8 Undesirable effects

Side effects of paracetamol are rare and usually mild, although haematological reactions have been reported. Skin rashes and hypersensitivity reactions occur occasionally. Overdosage with paracetamol if left untreated can result in severe, sometimes fatal liver damage and rarely, acute renal tubular necrosis. If serious side-effects occur, Lysoflam 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

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.

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 autoimmune 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 necroylsis and etheryma multiforme).

Diclofenac potassium: In patients taking Diclofenac Potassium tablets or other NSAIDs, the most frequently reported adverse experiences occurring in approximately 1% to 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: 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.

Other adverse reactions, which occur rarely are:

Body as a Whole: anaphylactic reactions, appetite changes, death

Cardiovascular System: arrhythmia, hypotension, myocardial infarction, palpitations, vasculitis

Digestive System: colitis, eructation, liver failure, 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.

Serratiopeptidase: Hypersensitivity reactions, such as rash or redness, may infrequently occur. If such reactions occur, Lysoflam should be discontinued.

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 Lysoflam.

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), Lysoflam should be discontinued. Hepatitis may occur with diclofenac without prodromal symptoms.

Use of Lysoflam in patients with hepatic porphyria may trigger an attack.

Haematological: Lysoflam may reversibly inhibit platelet aggregation. 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.
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

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 Lysoflam. 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.
Lysoflam should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

Female fertility: The use of Lysoflam 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 Lysoflam should be considered.

Paracetamol should be used with caution in patients with:

- impaired hepatic function
- impaired renal function

4.9 Overdose

Following an acute overdosage, toxicity may result. Symptoms include gastrointestinal irritation with erosion and hemorrhage or perforation, kidney damage, liver damage, heart damage, hemolytic anemia, agranulocytosis, thrombocytopenia, aplastic anemia, and meningitis. Other symptoms may include headache, dizziness, tinnitus, confusion, blurred vision, mental disturbances, skin rash, stomatitis, edema, reduced retinal sensitivity, corneal deposits, and hyperkalemia.

5. Pharmacological Particulars

PHARMACOLOGICAL CLASSIFICATION: A 2.8 Analgesic Combinations

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: analgesic, anti-inflammatory and anti-pyretic action.

Diclofenac potassium:

Lysoflam tablets contain the potassium salt of diclofenac, a nonsteroidal compound with pronounced and clinically demonstrable analgesic, anti-inflammatory and anti-pyretic properties.

Diclofenac is a potent inhibitor of prostaglandin biosynthesis and modulator of arachidonic acid release and uptake.

Lysoflam tablets have a rapid onset of action and are therefore suitable for the treatment of acute episodes of pain and inflammation.

In migraine attacks Lysoflam has been shown to be effective in relieving the headache and in improving the accompanying symptom of nausea.

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

Paracetamol:

The antipyretic effect of Paracetamol is attributed to its ability to inhibit COX in the brain where peroxide tone is low.

Recent evidence suggests inhibition of COX-3 (believed to be splice variant product of the COX-1 gene) could represent a primary central mechanism by which Paracetamol decreases pain and possibly fever.

Serratiopeptidase:

Serratiopeptidase is a proteolytic enzyme available for clinical use more than a decade. It binds to alpha-2-macroglobulin in the blood in the ratio of 1:1 which helps to mask its antigenicity but retains its enzymatic activity and is slowly, transferred to site of inflammation. Serratiopeptidase hydrolyses bradykinin, histamine and serotonin responsible for oedematic status. It reduces swelling improves microcirculation & expectoration of sputum etc. Thus it can be concluded that serratiopeptidase has anti-inflammatory, anti-oedemic and fibrinolytic activity and acts rapidly on localized inflammation.

Diclofenac, paracetamol and serratiopeptidase combined together provide effective relief from pain and inflammation.

5.2 Pharmacokinetic

Diclofenac Potassium

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. In some fasting volunteers, measurable plasma levels are observed within 10 minutes of dosing with Diclofenac Potassium. Peak plasma levels are achieve approximately 1 hour in fasting normal volunteers, with a range of 0.33 to 2 hours. Food has no significant effect on the extent of diclofenac absorption. However, there is usually a delay in the onset of absorption and a reduction in peak plasma levels of approximately 30%.

Distribution: Diclofenac is highly bound to plasma proteins (99.7%), chiefly albumin (99.4%)

Elimination: The total systemic clearance of diclofenac in plasma is 263 ± 56 ml/min (mean ± SD). The terminal half-life in plasma is 1-2 hours.

Repeated oral administration of Lysoflam for 8 days in daily doses of 50 mg t i d does not lead to accumulation of diclofenac in the plasma.

Approx. 60% of the dose administered is excreted in the urine in the form of metabolites, and less than 1% as unchanged substance. The remainder of the dose is eliminated as metabolites through the bile in the faeces.

Biotransformation: The biotransformation of diclofenac involves par tly glucuronidation of the intact molecule but mainly single and multiple hydroxylation followed by glucuronidation.

Characteristics in patients: The age of the patient has no influence on the absorption, metabolism, or excretion of diclofenac.

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 <10 ml/min the theoretical steady-state plasma levels of metabolites are about four times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.
In the presence of impaired hepatic function (chronic hepatitis, non-decompensated cirrhosis) the kinetics and metabolism are the same as for patients without liver disease.

Paracetamol

Paracetamol is rapidly and almost completely absorbed from gastrointestinal tract with peak plasma concentrations (Cmax) occurring about 10 to 60 minutes after oral administration. Plasma protein binding is negligible at usual therapeutic concentration but increases with increasing concentrations. Acetaminophen is relatively uniformly distributed throughout most body fluids. The plasma half-life (t1/2) 2-3 hours and the effect after oral dose lasts for 3-5 hours. Paracetamol is metabolized predominantly in liver and excreted in the urine mainly as glucoronides and sulfate conjugate. Less than 5% is excreted unchanged.

Serratiopeptidase

Serratiopeptidase when consumed in unprotected form is destroyed by acid in the stomach. However, enteric coated granules, enable the enzyme to pass through the stomach unchanged and be absorbed in the intestine. It is found negligibly in urine suggesting that it is transported directly from the intestine into the blood stream.

6. Pharmaceutical Particulars

6.1 List of Excipients

Raw Material
Maize Starch BP
Microcrystalline cellulose BP
Magnesium stearate BP
Purified Talc BP
Color Tartrazine IH
Sodium Starch Glycollate BP

Methyl Hydroxybenzoate BP
Propyl Hydroxybenzoate BP
Opadry II (85G52193) Yellow IH
Purified Water BP

6.2 Incompatibilities
Not applicable

6.3 Shelf Life: 24 Months

6.4 Special Precautions for Storage:
Store in a dry place, below 30°C. Protect from light.
Keep out of reach of children

6.5 Nature and Contents of Container: Alu–PVC Blister pack of 1 x 10 Tablets

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

Marketing Authorisation Holder:

Cachet Pharmaceuticals Pvt. Ltd
415, Shah Nahar Industrial Estate,
Dr. E. Moses Road, Worli, Mumbai-400 018,
Maharashtra, India.

Manufacturer's Name and Address:
Cachet Pharmaceuticals PVT. LTD.
Village Thana, Baddi, Dist. Solan,
Himachal Pradesh-Pin – 173 205, India.

8.Marketing Authorization Numbers
Rwanda FDA-HMP-MA-1056.

9. Date of First Authorization/ Renewal of the Authorization
28/02/2024

10. Date of Revision of the Text
29.02.2024