1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

INFLANIL, Paracetamol 500 mg and Diclofenac Sodium 50 mg Caplets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated caplet contains:
Paracetamol BP 500 mg
Diclofenac Sodium BP 50 mg
Excipients Q.S.
Approved colours used

3. PHARMACEUTICAL FORM

Uncoated caplet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

INFLANIL is a combination medicine used for the symptomatic treatment of acute musculoskeletal pain and inflammation in patients with osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and sprain.

4.2 Posology and method of administration

One caplet to be taken with food, two or three times daily.
Caplet should be swallowed whole, not chewed or as directed by the Physician.

4.3 Contraindications

INFLANIL are contraindicated in patients with the following conditions:

- Hypersensitivity to diclofenac and/ or paracetamol and/or other constituents.
- Patients with active peptic ulcer/haemorrhage or perforation or who have active GI bleeding or other active bleedings, e.g. cerebrovascular bleedings.
- Pregnant women and in women planning a pregnancy.
- Women of childbearing potential who are not using effective contraception
- Patients with a known hypersensitivity to diclofenac, acetylsalicylic acid, other NSAIDs, misoprostol, other prostaglandins, or any other ingredient of the product.
- Patients in whom attacks of asthma, urticaria or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs.
- Treatment of peri-operative pain in the setting of CABG surgery.
- Patients with severe renal and hepatic failure.
- Established congestive heart failure (NYHA II–IV), ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

4.4 Special warnings and precautions for use

Diclofenac Sodium

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 (GI) events.

Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated.
NSAIDs, including diclofenac, may be associated with increased risk of gastro-intestinal anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac after gastro-intestinal surgery.
As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with diclofenac, regular monitoring of hepatic function is indicated as a precautionary measure.
If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (eosinophilia, rash), diclofenac should be discontinued.
Hepatitis may occur with diclofenac without prodromal symptoms.
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.
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 diclofenac.
In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis
Patients with congestive heart failure (NYHA-1) or patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration. As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.
During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of the blood count is recommended.
Diclofenac may reversibly inhibit platelet aggregation (see anticoagulants in section 4.5). Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.
Female fertility: The use of Diclofenac may impair female fertility and is not recommended in women attempting to conceive. In women who may have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Diclofenac should be considered.

Paracetamol

Where analgesics are used long-term (>3 months) with administration every two days or more frequently, headache may develop or worsen. Headache induced by overuse of analgesics (MOH medication-overuse headache) should not be treated by dose increase. In such cases, the use of analgesics should be discontinued in consultation with the doctor.
Care is advised in the administration of Paracetamol to patients with alcohol dependency (see section 4.9), severe renal or severe hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.
Label Warnings:
Do not exceed the recommended dose
If symptoms persist consult your doctor
Keep out of the sight and reach of children
Do not take with any other Paracetamol-containing products.

Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage.
or if leaflet present: Immediate medical advice should be sought in the event of an overdose, even if you feel well.

4.5 Interaction with other medicinal products and other forms of interaction

Diclofenac Sodium

Aspirin: When diclofenac 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: Diclofenac, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Therefore, concomitant therapy with diclofenac may increase cyclosporine's nephrotoxicity.

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 postmarketing observations, have shown that diclofenac 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. Steady-state plasma lithium and digoxin levels may be increased and ketoconazole levels may be decreased.

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 metabolised by cytochrome (CY) 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.

Other Interactions

There is a possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Cases of hypo- and hyperglycaemia have been reported when diclofenac was associated with antidiabetic agents.

Concomitant use with other NSAIDs or with corticosteroids may increase the frequency of side effects generally.

NSAIDs can reduce the efficacy of diuretics and other antihypertensive drugs, including ACE inhibitors, angiotensin II antagonists (AIIA) and beta-blockers.

In patients with impaired renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of an ACE inhibitor or an AIIA and/or diuretics with a cyclo-oxygenase inhibitor can increase the deterioration of the renal function, including the possibility of acute renal failure, which is usually reversible.
Antacids may delay the absorption of diclofenac. Magnesium-containing antacids have been shown to exacerbate misoprostol-associated diarrhoea.
Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.
NSAIDs should not be used for 8–12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
Voriconazole increased Cmax and AUC of diclofenac (50 mg single dose) by 114% and 78%, respectively.
Paracetamol
The speed of absorption of paracetamol may be increased by metoclopramide or domperidone. However, concurrent use need not be avoided.
The speed of absorption of paracetamol is reduced by colestyramine. Therefore, colestyramine should not be taken within 1 hour if maximal analgesia is required.
The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.
Restriction or avoidance of concomitant regular paracetamol use should be followed with imatinib.
Chloramphenicol plasma concentration is increased when given with paracetamol.

4.6 Fertility, pregnancy and lactation

Diclofenac Sodium

Teratogenic Effects: Pregnancy Category C
Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.
Non-Teratogenic Effects: Because of the known effects of NSAIDs on the foetal CV system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Paracetamol

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of their doctor regarding its use.
A large amount of data on pregnant women indicates neither mal-formative, nor foeto-/neonatal toxicity. Paracetamol can be used during pregnancy if clinically needed; however, it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.
In late pregnancy, as with other NSAIDs, INFLANIL should be avoided because they may cause premature closure of the ductus arteriosus.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness or other central nervous system disturbances while taking NSAIDs should refrain from driving or operating machinery.

4.8 Undesirable effects

Diclofenac Sodium

In patients taking diclofenac sodium tablets, or other NSAIDs, the most frequently reported adverse experiences occurring in approximately 1–10% of patients are as follows:

GI Events: These include abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, GI ulcers (gastric/duodenal) and vomiting.

Other: Abnormal renal function, anaemia, dizziness, oedema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes and tinnitus.

Additional adverse experiences reported occasionally include the following:

Body as a Whole: fever, infection, sepsis

CV System: congestive heart failure, hypertension, tachycardia, syncope

Digestive System: dry mouth, oesophagitis, gastric/peptic ulcers, gastritis, GI bleeding, glossitis, haematemesis, hepatitis, jaundice

Haemic and Lymphatic System: ecchymosis, eosinophilia, leucopaenia, melaena, purpura, rectal bleeding, stomatitis, thrombocytopaenia

Metabolic and Nutritional: weight changes

Nervous System: anxiety, asthenia, confusion, depression, dream abnormalities, drowsiness, insomnia, malaise, nervousness, paraesthesia, somnolence, tremors, vertigo

Respiratory System: asthma, dyspnoea

Skin and Appendages: alopecia, photosensitivity, sweating increased

Special Senses: blurred vision

Urogenital System: cystitis, dysuria, haematuria, interstitial nephritis, oliguria/polyuria, proteinuria, renal failure

Other adverse reactions, which occur rarely, are as follows:

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

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

Digestive System: colitis, eructation, fulminant hepatitis with and without jaundice, liver failure, liver necrosis, pancreatitis.

Haemic and Lymphatic System: agranulocytosis, haemolytic anaemia, aplastic anaemia, lymphadenopathy, pancytopaenia

Metabolic and Nutritional: hyperglycaemia

Nervous System: convulsions, coma, hallucinations, meningitis

Respiratory System: respiratory depression, pneumonia

Skin and Appendages: angio-oedema, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, urticaria

Special Senses: conjunctivitis, hearing impairment

Nicolau' s syndrome, also known as livedo-like dermatitis or embolia cutis medicamentosa, is a rare complication reported following intramuscular diclofenac sodium injection.

Paracetamol

The information below lists reported adverse reactions, ranked using the following frequency classification: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Immune System Disorders

Hypersensitivity, including skin rash, may occur

Not Known: anaphylactic shock, angio-oedema

Blood and Lymphatic System Disorders

Not Known: blood dyscrasias, including thrombocytopaenia and agranulocytosis

Skin and Subcutaneous Disorders

Very rare cases of serious skin reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis, and fixed drug eruption have been reported.

4.9 Overdose

Diclofenac Sodium: Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, confusion, disorientation, excitation, coma, tinnitus, fainting or convulsions, vomiting, headache, dizziness and epigastric pain, which are generally reversible with supportive care. GI complaints, including GI 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. In the case of significant poisoning, acute renal failure and liver damage are possible.

Patients should be managed by symptomatic and supportive care following a NSAID overdose. There are no specific antidotes. Emesis and/or activated charcoal (60–100 g in adults, 1–2 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 (5–10 times the usual dose). Forced diuresis, alkalinisation of urine, haemodialysis or haemoperfusion may not be useful due to high protein-binding.

Management of acute poisoning with NSAIDs essentially consists of supportive and symptomatic measures. It is reasonable to take measures to reduce absorption of any recently consumed drug by forced emesis, gastric lavage or activated charcoal. Induced diuresis may be beneficial because diclofenac and misoprostol metabolites are excreted in the urine, provided that the patient does not develop renal failure at diclofenac overdose. Special measures such as haemodialysis or haemoperfusion are probably unlikely to be helpful in accelerating the elimination of diclofenac, due to the high protein binding and extensive metabolism.

Paracetamol: Liver damage is possible in adults who have taken 10 g or more of paracetamol. Ingestion of 5 g or more of paracetamol may lead to liver damage if the patient has risk factors.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Diclofenac Sodium

Pharmacotherapeutic group (ATC code): M01AB55

Diclofenac sodium is a NSAID that has been shown to have anti-inflammatory and analgesic properties and is effective in treating the signs and symptoms of arthritic conditions.

Paracetamol

ATC code: N02B E01, Other analgesics and antipyretics

Analgesic: The mechanism of analgesic action has not been fully determined. Paracetamol may act predominately by inhibiting prostaglandin synthesis in the central nervous system and, to a lesser extent, through a peripheral action by blocking pain-impulse generation.

The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation.

Antipyretic: Paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat-regulation centre to produce peripheral vasodilation, resulting in increased blood flow through the skin, sweating and heat loss. The central action probably involves inhibition of prostaglandin synthesis in the hypothalamus. The drug has no effect

on the CV and respiratory systems and unlike salicylates, it does not cause gastric irritation or bleeding.
Paracetamol has analgesic and antipyretic actions but it has no useful anti- inflammatory properties.

5.2 Pharmacokinetic properties

Diclofenac Sodium

Absorption: Diclofenac is 100% absorbed after oral administration compared to intravenous (IV) administration as measured by urine recovery. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available. Food has no significant effect on the extent of diclofenac absorption. However, there is usually a delay in the onset of absorption of 1–4.5 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 sulphation 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-hydroxyand 3'-hydroxy-diclofenac. In patients with renal dysfunction, peak concentrations of the metabolites, 4'-hydroxy- and 5-hydroxy-diclofenac, were approximately 50% and 4% of the parent compound after single oral dosing compared with 27% and 1%, respectively, in normal healthy subjects.
Excretion: Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulphate 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.

Paracetamol

Paracetamol is readily absorbed from the GI tract, with peak plasma levels occurring about 30 minutes to 2 hours after ingestion. It is metabolised in the liver (90–95%) and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted unchanged. The elimination half-life of paracetamol varies from about 1 to 4 hours. Plasma protein-binding is negligible at usual therapeutic doses but increases with increasing concentrations.
A minor hydroxylated metabolite (N-acetyl-p-benzoquinoneimine), which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione, may accumulate following paracetamol overdosage and cause liver damage.

The time to peak plasma concentration of paracetamol is 0.5–2 hours, the time to peak effect 1–3 hours, and the duration of action is 3–4 hours.

5.3 Preclinical safety data
Not Applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Maize Starch
Methyl Paraben
Propyl Paraben
Purified Water
Sodium Starch Glycolate
Color Ponceau 4R
Colloidal Silicon Dioxide
Talc
Magnesium Stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store below 30°C. Protect from light and moisture.

6.5 Nature and contents of container
2 x 10 Alu/PVC blister

6.6 Special precautions for disposal and other handling
Keep the medicine out of reach of children.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

MARKETING AUTHORIZATION HOLDER:
SAM PHARMACEUTICAL LIMITED
8/9, Oyadiran Estate, Sabo, Yaba, Lagos, Nigeria.

MANUFACTURING SITE ADDRESS:
UNIZA LIFECARE PRIVATE LIMITED
SR. No. 919/7, (Old SR. No.404), Kadi-Detroj Road, Balasar,
Tal: Kadi, Dist: Mehsana, Gujarat. PIN: 382715, INDIA.

8. MARKETING AUTHORIZATION NUMBER
A4 – 6464

9. DATE OF FIRST REGISTRATION / RENEWAL OF THE REGISTRATION
Change of Manufacturing Site

10. DATE OF REVISION OF THE TEXT
30th July 2027