1.3 Product Information
1.3.1 Summary of product characteristics (SmPC)
1. 3.1.1 Name of the drug product:

ANIMOL
(Diclofenac Potassium Tablets 50mg)

1.3. 1.2 Qualitative and quantitative composition:
Each Uncoated Tablet Contains:
Diclofenac Potassium BP……50mg
Excipients.……q.s.
Approved Colour Used

Sr. No.	Ingredients	Specifi-cation	Label Claim / Tablet (In mg)	Over-ages added (In %)	Qty. / Tablet (In mg)	Reason for Function
a)	**Dry Mixing (White Part)**					
1.	Diclofenac Potassium	BP	50.00	NA	25.64	Medicament
2.	Calcium Hydrogen Phosphate Dihydrate	BP	NA	NA	50.90	Diluent
3.	Calcium Carbonate	BP	NA	NA	51.30	Diluent
4.	Maize Starch	BP	NA	NA	103.00	Diluent
5.	Povidone K30	BP	NA	NA	0.91	Binder
b)	**Dry Mixing (Yellow Part)**					
6.	Diclofenac Potassium	BP	50.00	NA	8.12	Medicament
7.	Calcium Hydrogen Phosphate Dihydrate	BP	NA	NA	17.70	Diluent
8.	Calcium Carbonate	BP	NA	NA	17.15	Diluent
9.	Maize Starch	BP	NA	NA	36.25	Diluent
10.	Tartrazine	IHS	NA	NA	0.09	Colour
11.	Povidone K30	BP	NA	NA	0.62	Binder
c)	**Dry Mixing (Pink Part)**					
12.	Diclofenac Potassium	BP	50.00	NA	8.12	Medicament
13.	Calcium Hydrogen Phosphate Dihydrate	BP	NA	NA	17.70	Diluent
14.	Calcium Carbonate	BP	NA	NA	17.15	Diluent
15.	Maize Starch	BP	NA	NA	36.25	Diluent
16.	Erythrosine	IHS	NA	NA	0.09	Colour
17.	Povidone K30	BP	NA	NA	0.62	Binder
d)	**Dry Mixing (Blue Part)**					
18.	Diclofenac Potassium	BP	50.00	NA	8.12	Medicament
19.	Calcium Hydrogen Phosphate Dihydrate	BP	NA	NA	17.70	Diluent
20.	Calcium Carbonate	BP	NA	NA	17.15	Diluent

21.	Maize Starch	BP	NA	NA	36.25	Diluent
22.	Brilliant Blue FCF	IHS	NA	NA	0.09	Colour
23.	Povidone K30	BP	NA	NA	0.62	Binder
e)	**Binder Preparation (White Part)**					
24.	Maize starch	BP	NA	NA	6.55	Binder
25.	Gelatin (Gelling grade)	BP	NA	NA	1.97	Binder
26.	Methyl hydroxybenzoate	BP	NA	NA	0.12	Preservative
27.	Propyl hydroxybenzoate	BP	NA	NA	0.04	Preservative
28.	Purified water	BP	NA	NA	---	Vehicle
f)	**Binder Preparation (Yellow Part)**					
29.	Maize starch	BP	NA	NA	3.39	Binder
30.	Gelatin (Gelling grade)	BP	NA	NA	0.78	Binder
31.	Methyl hydroxybenzoate	BP	NA	NA	0.06	Preservative
32.	Propyl hydroxybenzoate	BP	NA	NA	0.03	Preservative
33.	Purified water	BP	NA	NA	---	Vehicle
g)	**Binder Preparation (Pink Part)**					
34.	Maize starch	BP	NA	NA	3.39	Binder
35.	Gelatin (Gelling grade)	BP	NA	NA	0.78	Binder
36.	Methyl hydroxybenzoate	BP	NA	NA	0.06	Preservative
37.	Propyl hydroxybenzoate	BP	NA	NA	0.03	Preservative
38.	Purified water	BP	NA	NA	---	Vehicle
h)	**Binder Preparation (Blue Part)**					
39.	Maize starch	BP	NA	NA	3.39	Binder
40.	Gelatin (Gelling grade)	BP	NA	NA	0.78	Binder
41.	Methyl hydroxybenzoate	BP	NA	NA	0.06	Preservative
42.	Propyl hydroxybenzoate	BP	NA	NA	0.03	Preservative
43.	Purified water	BP	NA	NA	---	Vehicle
i)	**Lubrication**					
44.	Purified Talc	BP	NA	NA	6.00	Glidant
45.	Magnesium Stearate	BP	NA	NA	4.00	Lubricant
46.	Croscarmellose Sodium	BP	NA	NA	6.00	Disintegrant
47.	Colloidal Anhydrous Silica	BP	NA	NA	1.00	Glidant
48.	Maize Starch	BP	NA	NA	10.00	Disintegrant
	Average Weight of Uncoated Tablet (In mg)				**520.00**	

1. 3.1.3 Pharmaceutical form: Uncoated tablet
Description: Multi-coloured, round shaped, biconvex, uncoated tablet, plain on both sides.

1.3.1.4 Clinical Particulars

1.3.1.4.1 Therapeutic indications:

ANIMOL Tablets are indicated in -

Rheumatoid arthritis, Osteoarthrosis, Low back pain, Migraine attacks, Acute musculo-skeletal disorders and trauma such as periarthritis (especially frozen shoulder), tendinitis, tenosynovitis, bursitis, sprains, strains and dislocations; relief of pain in fractures, Ankylosing spondylitis, Acute gout, Control of pain and inflammation in orthopaedic, dental and other minor surgery, Pyrophosphate arthropathy and associated disorders.

1.3.1.4.2 Posology and method of administration

Route: Oral

For treatment of pain or Primary Dysmenorrhea

The recommended dosage is 50 mg three times a day.

With experience, physicians may find that in some patients an initial dose of 100 mg of followed by 50-mg doses, will provide better relief.

For the relief of Osteoarthritis

The recommended dosage is 100-150 mg/day in divided doses, 50 mg twice a day or three times a day.

For the relief of Rheumatoid Arthritis

The recommended dosage is 150-200 mg/day in divided doses, 50 mg three times a day or four times a day.

1.3.1.4.3 Contraindications

ANIMOL (Diclofenac potassium Tablets 50mg) are contraindicated in:

- Patients with known hypersensitivity to Diclofenac Potassium or to any of the excipients use in the formulation.
- Active, gastric or intestinal ulcer, bleeding or perforation.
- Active or history of recurrent peptic ulcer / haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema, or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Severe heart failure, hepatic failure and renal failure
- History of gastro-intestinal bleeding or perforation, relating to previous NSAID therapy.
- During the last trimester of pregnancy.

1.3.1.4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

The use of Diclofenac potassium with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects.

Elderly

Caution is indicated in the elderly on basic medical grounds. The elderly have increased frequency of adverse reactions to NSAIDs especially gastro intestinal bleeding and perforation which may be fatal. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.

Gastrointestinal

Close medical surveillance is imperative in patients with symptoms indicative of gastrointestinal disorders, with a history suggestive of gastric or intestinal ulceration, bleeding or perforation, 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) particularly in the initial stages of treatment.

GI bleeding (haematemesis, melaena), ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events. They generally have more serious consequences in the elderly.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly. These patients should commence and maintain 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, or other drugs likely to increase gastrointestinal risk.

Caution should be advised in patients receiving concomitant medications which increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin.

When GI bleeding or ulceration occurs in patients receiving diclofenac potassium, the treatment should be withdrawn.

NSAID

Hypersensitivity reactions

As with other non-steroidal anti-inflammatory drugs, allergic reactions, including anaphylactic/anaphylactoid reactions, can occur without earlier exposure to the drug.

Infection

Like other NSAIDs, Diclofenac Potassium tablets may mask the signs and symptoms of infection due to their pharmacodynamic properties.

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.

Cardiovascular, Renal and Hepatic Impairment:

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure.

As fluid retention and oedema have been reported in association with NSAIDs 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 those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery. Monitoring of renal function is recommended as a precautionary measure when using diclofenac in such cases. Discontinuation therapy is usually followed by recovery to the pre-treatment state.

Hepatic

Close medical surveillance is required when prescribing diclofenac to patients with impairment of hepatic function as their condition may be exacerbated.

As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with Diclofenac, regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), Diclofenac Potassium tablets should be discontinued.

Hepatitis may occur without prodromal symptoms.

Use of Diclofenac Potassium tablets in patients with hepatic porphyria may trigger an attack.

Haematological

Diclofenac Potassium tablets 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 long term treatment with non-steroidal, anti-inflammatory agents should be monitored as a precautionary measure eg renal function, hepatic function (elevation of liver enzymes may occur) and blood counts. This is particularly important in the elderly.

Respiratory disorders

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so called intolerance to analgesics / analgesics asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria.

Like other drugs that inhibit prostaglandin synthetase activity, diclofenac sodium and other 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 and with significant risk factors for cardiovascular events (e.g.,, 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.

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. Patients appear to be at highest risk for 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. Diclofenac potassium should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Impaired female fertility

The use of Diclofenac Potassium tablets 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 Potassium tablets should be considered.

1.3.1.4.5 Interaction with other medicinal products and other forms of interaction Aspirin

When diclofenac potassium tablets are 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 tablets, 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 tablets are 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 postmarketing observations, have shown that Diclofenac Potassium tablets 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.

1.3.1.4.6 Pregnancies and Lactation:

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and or cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1% up to approximately 1.5%.

The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has shown to result in increased pre-and post-implantation loss and embryo-foetal lethality.

In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during organogenetic period. NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus. If diclofenac is used by a woman attempting to conceive, or during the 1st or 2nd trimesters of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis
The mother and the neonate, at the end of the pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses
- inhibition of uterine contractions resulting in delayed or prolonged labour
Consequently, diclofenac is contra-indicated during the third trimester of pregnancy.

Lactation
Like other NSAIDs, diclofenac passes into breast milk in small amounts. Therefore Diclofenac should not be administered during breast feeding in order to avoid undesirable effects in the infant.

1.3.1.4.7 Effects on the ability to drive and use machines
Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

1.3.1.4.8 Undesirable effects
- Cardiovascular Thrombotic Events
- GI Bleeding, Ulceration and Perforation
- Hepatotoxicity
- Hypertension
- Heart Failure and Edema
- Renal Toxicity and Hyperkalemia
- Anaphylactic Reactions
- Serious Skin Reactions
- Hematologic Toxicity

1.3.1.4.9 Overdoses
Symptoms
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.
Treatment
Patients should be managed by symptomatic and supportive care following an 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.

1.3.1.5 Pharmacological properties
1.3.1.5.1 Pharmacodynamic properties
Diclofenac Potassium tablets contain the potassium salt of diclofenac, a non-steroidal compound with pronounced and clinically demonstrable analgesic, anti-inflammatory and anti-pyretic properties. Diclofenac is a potent inhibitor of prostaglandin bio-synthesis and modulator of

arachidonic acid release and uptake. Diclofenac Potassium tablets have a rapid onset of action and are, therefore, suitable for the treatment of acute episodes of pain and inflammation. In migraine attacks Diclofenac Potassium 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.

1.3.1.5.2 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). In some fasting volunteers, measurable plasma levels are observed within 10 minutes of dosing with Diclofenac Potassium Tablets. Peak plasma levels are achieved approximately 1 hour in fasting normal volunteers, with a range of .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%.

Table 1: Pharmacokinetic Parameters for Diclofenac

PK PARAMETER	NORMAL HEALTHY ADULTS (20-52 YEARS)	
	Mean	**Coefficient Of Variation (%)**
Absolute Bioavailability (%) [N = 7]	55	40
Tmax (hr) [N = 65]	1.0	76
Oral Clearance (CL/F; mL/min) [N = 61]	622	21
Renal Clearance (% unchanged drug in urine) [N = 7]	< 1	—
Apparent Volume of Distribution (V/F; L/kg) [N = 61]	1.3	33
Terminal Half-life (hr) [N = 48]	1.9	29

Distribution:

The apparent volume of distribution (V/F) of Diclofenac Potassium is 1.3 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 mcg/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 CYP2C9. Both diclofenac and its oxidative metabolites undergo glucuronidation or sulfation followed by biliary excretion. Acylglucuronidation mediated by UGT2B7 and oxidation mediated by CYP2C8 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.
Elimination:
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.

1.3.1.5.3 Preclinical safety Data

Relevant information on the safety of Diclofenac potassium tablets 50mg is included in other sections of the Summary of Product Characteristics.

1.3.1.6 Pharmaceutical particulars

1.3.1.6.1 List of excipients

- Calcium Hydrogen Phosphate Dihydrate
- Calcium carbonate
- Maize Starch
- Povidone K30
- Tartrazine
- Erythrosine
- Brilliant Blue FCF
- Gelatin (Gelling grade)
- Methyl hydroxybenzoate
- Propyl hydroxybenzoate
- Purified talc
- Magnesium stearate
- Colloidal anhydrous silica
- Croscarmellose sodium

1.3.1.6.2 Incompatibilities

Not applicable

1.3.1.6.3 Shelf life

36 months

1.3.1.6.4 Special precautions for storage

Store below 30°C in a dry & dark place.
Keep all medicines out of reach of children.

1.3.1.6.5 Nature and contents of container

Primary packing: 12 Tablets in an ALU-PVC blister.
Secondary packing: 1 Blister is packed in an inner carton along with leaflet.
Tertiary packing: 20 Inner cartons are packed in an outer carton. Shrink individual outer carton. Such 48 Shrinks are packed in a 5 Ply corrugated box sealed with BOPP tape & strap with strapping roll.

1.3.1.6.5 Special precautions for disposal and other handling
None.

1.3.1.7 Applicant / Manufacturer

Applicant

Applicant name and address	**M/s. ANISUN PHARMACEUTICALS CO. NIG. LTD.** No. 29, Heritage Avenue Omgba phase 11, Onitsha, Anambra State.
Contact person's phone number	
Contact person's email	

Manufacturer

Manufacturer name and address	**M/s. IMPULSE PHARMA PVT. LTD.** J-201, J-202/1 , MIDC Tarapur, Boisar, Dist. Palghar - 401506, Maharashtra State, India.
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