1.1 Name of the medicinal product:

DIKTAZ
(Diclofenac Potassium Tablets 50 mg)

1.3.1.2 Qualitative and quantitative composition:

Sr. No.	Ingredients	Specifi-cation	Label Claim / Tablet (In mg)	Over-ages added (In %)	Qty. / Tablet (In mg)	Reason For Function
Sifting / Dry Mixing						
1.	Diclofenac Potassium	BP	50.00	NA	50.00	Medicament
2.	Maize Starch	BP	NA	NA	338.61	Diluent
3.	Calcium Carbonate	BP	NA	NA	85.72	Diluent
4.	Calcium Hydrogen Phosphate Dihydrate	BP	NA	NA	103.50	Diluent
5.	Microcrystalline Cellulose	BP	NA	NA	138.81	Disintegrant
6.	Tartrazine	IH	NA	NA	0.60	Colouring agent
7.	Sodium Starch Glycolate	BP	NA	NA	10.21	Disintegrant
8.	Sodium Lauryl Sulfate	BP	NA	NA	4.00	Disintegrant
Binder Preparation						
9.	Maize Starch	BP	NA	NA	45.00	Binder
10.	Povidone K 30	BP	NA	NA	20.00	Binder
11.	Methyl Hydroxybenzoate	BP	NA	NA	0.50	Preservative
12.	Propyl Hydroxybenzoate	BP	NA	NA	0.30	Preservative
13.	Purified Water	BP	NA	NA	--	Vehicle
Lubrication						
14.	Purified Talc	BP	NA	NA	10.21	Glidant
15.	Magnesium Stearate	BP	NA	NA	6.80	Lubricant
16.	Sodium Starch Glycolate	USP	NA	NA	17.02	Disintegrant
17.	Colloidal Anhydrous silica	BP	NA	NA	3.40	Glidant
18.	Sodium Lauryl Sulfate	BP	NA	NA	15.32	Disintegrant
	Average Weight of Uncoated Tablet (In mg)				**850.00 mg**	

1.3.1.3 Pharmaceutical form: Uncoated Tablets
Description: Yellow coloured, capsule shaped biconvex uncoated tablet breakline on one side and plain on other side.

1.3.1.4 Clinical Particulars
1.3.1.4.1 Therapeutic indications
DIKTAZ (Diclofenac Potassium Tablets 50mg) 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

Method of Administration:
Adults
The recommended daily dose is 100-150mg in two or three divided doses. For milder cases, 75-100mg daily in two or three divided doses is usually sufficient.

In migraine an initial dose of 50mg should be taken at the first signs of an impending attack. In cases where relief 2 hours after the first dose is not sufficient, a further dose of 50mg may be taken. If needed, further doses of 50mg may be taken at intervals of 4-6 hours, not exceeding a total dose of 200mg per day.

Pediatric population
For children over 14 years of age, the recommended daily dose is 75-100mg in two or three divided doses. Diclofenac Potassium Tablets are not recommended for children under 14 years of age.

Elderly
In Elder patients it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight (see also precautions) and the patient should be monitored for GI bleeding during NSAID therapy.

1.3.1.4.3 Contraindications
DIKTAZ (Diclofenac Potassium Tablets 50mg) are contraindicated in:
- Patients with known hypersensitivity to Diclofenac Potassium or to any of the excipients used in the formulation.
- Active, gastric or intestinal ulcer, bleeding or perforation.
- History of gastrointestinal bleeding or perforation, relating to previous NSAID therapy.
- 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.

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 effect:
As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing diclofenac in patients with symptoms indicative of gastrointestinal disorders, or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation. The risk of GI bleeding, ulceration or perforation is higher with increasing diclofenac doses and in patients with a history of ulcer, particularly if complicated with

haemorrhage or perforation.
The elderly have increased frequency of adverse reactions to NSAIDs especially gastro intestinal bleeding and perforation which may be fatal
To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose.
Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low dose acetylsalicylic acid (ASA/aspirin or medicinal products likely to increase gastrointestinal risk.
Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding).
Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors (SSRIs) or anti-platelet agents such as acetylsalicylic acid.
Close medical surveillance and caution should be exercised in patients with ulcerative colitis, or with Crohn's disease as these conditions may be exacerbated.
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.
Hepatic effects:
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 should be discontinued.
Hepatitis may occur with diclofenac without prodromal symptoms.
Caution is called for when using diclofenac in patients with hepatic porphyria, since it may trigger an attack.

Renal effects:
As fluid retention and oedema have been reported in association with doclofenac therapy, 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.

Skin effects:
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 Diclofenac. 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. Diclofenac should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

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 and cerebrovascular effects:
Patients with congestive heart failure (NYHA-I) 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.
Appropriate monitoring and advice are required for patients with a history of hypertension and congestive heart failure (NYHA-I) as fluid retention and oedema have been reported in association with NSAID therapy, including diclofenac.
Clinical trial and epidemiological data consistently point towards increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (150mg daily) and in long term treatment.
Patients should remain alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. Patients should be instructed to see a physician immediately in case of such an event.

Haematological effects:
Use of diclofenac are recommended only for short term treatment.
During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of the blood count is recommended.
Diclofenac may reversibly inhibit platelet aggregation. Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.
Pre-existing asthma:
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.
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.

1.3.1.4.5 Interaction with other medicinal products and other forms of interaction
Lithium: If used concomitantly, diclofenac may increase plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

Digoxin: If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.
Diuretics and antihypertensive agents: Concomitant use of diclofenac with diuretics and antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis.
Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of

concomitant therapy periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity.

Drugs known to cause hyperkalemia: Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently.

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding. Although clinical investigations do not appear to indicate that diclofenac has an influence on the effect of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulant concomitantly. Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other nonsteroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

Other NSAIDs including cyclooxygenase-2 selective inhibitors and corticosteroids: Co-administration of diclofenac with other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration. Avoid concomitant use of two or more NSAIDs.

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of SSRI's may increase the risk of gastrointestinal bleeding.

Antidiabetics: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However there have been isolated reports of hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Methotrexate: Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increase. Cases of serious toxicity have been reported when methotrexate and NSAIDs, including diclofenac are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.

Ciclosporin: Diclofenac, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.

Tacrolimus: Possible increased risk of nephrotoxicity when diclofenac are given with tacrolimus. This might be mediated through renal antiprostagladin effects of both NSAID and calcineurin inhibitor.

Quinolone antibacterials: Convulsions may occur due to an interaction between quinolones and diclofenac. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.

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

Colestipol and cholestyramine: These agents can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/ cholestyramine.

Cardiac glycosides: Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

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

Zidovudine:

Increased risk of haematological toxicity when diclofenac are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

1.3.1.4.6 Pregnancy 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 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

Adverse reactions

Adverse reactions are ranked under the heading of frequency, the most frequent first, using the following convention:

very common: (>1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1,000, <1/100); rare (≥1/10,000, <1/1000); very rare (<1/10,000); Unknown: cannot be estimated from available data.

The following undesirable effects include those reported with other short-term or long-term use. **Blood and lymphatic system disorders**	
Very rare	Thrombocytopenia, leucopoenia, anaemia

	(Including haemolytic and aplastic anaemia), agranulocytosis.
Immune system disorders	
Rare	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).
Very rare	Angioneurotic oedema (including face oedema).
Psychiatric disorders	
Very rare	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders	
Common	Headache, dizziness.
Rare	Somnolence, tiredness.
Very rare	Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.
Unknown	Confusion, hallucinations, disturbances of sensation malaise
Eye disorders	
Very rare	Visual disturbance, vision blurred, diplopia.
Unknown	Optic neuritis.
Ear and labyrinth disorders	
Common	Vertigo.
Very rare	Tinnitus, hearing impaired.
Cardiac disorders	
Uncommon	Myocardial infarction, cardiac failure, palpitations, chest pain.
Unknown	Kounis syndrome
Vascular disorders	
Very rare	Hypertension, hypotension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Rare	Asthma (including dyspnoea).
Very rare	Pneumonitis.
Gastrointestinal disorders	
Common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.
Rare	Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer with or without bleeding or perforation (sometimes fatal particularly in the elderly).
Very rare	Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis.
Unknown	Ischaemic colitis
Hepatobiliary disorders	
Common	Transaminases increased.
Rare	Hepatitis, jaundice, liver disorder.
Very rare	Fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders	

Common	Rash.
Rare	Urticaria.
Very rare	Bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus.
Renal and urinary disorders	
Very rare	Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.
General disorders and administration site conditions	
Rare	Oedema
Reproductive system and breast disorders	
Very rare	Impotence

1.3.1.4.9 Overdose

Symptoms

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, dizziness, disorientation, excitation, coma, drowsiness, tinnitus, fainting, occasionally and convulsions. In rare cases of significant poisoning acute renal failure and liver damage are possible.

Treatment

Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Good urine output should be ensured. Special measures such as forced diuresis, dialysis or haemo-perfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to high protein binding and extensive metabolism.

Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Frequent or prolonged convulsions should be treated with intravenous diazepam. Supportive measures should be given for complications such as hypotension, renal failure, gastrointestinal disorder, and respiratory depression.

1.3.1.5 Pharmacological properties

1.3.1.5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-steroidal anti-inflammatory drug (NSAID).

ATC code: M01AB05

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 biosynthesis and a 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 tablets have 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
Preclinical data reveal no special hazard for humans based on conventional studies on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

1.3.1.6 Pharmaceutical particulars
1.3.1.6.1 List of excipients
Maize starch, Calcium Carbonate, Calcium Hydrogen Phosphate Dihydrate, Microcrystalline Cellulose, Tartrazine, Sodium Starch Glycolate, Sodium Lauryl Sulphate, Povidone K 30, Methyl hydroxybenzoate, Propyl hydroxybenzoate, Purified talc, Magnesium stearate, Colloidal anhydrous silica, Purified Water.

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: 1x10 Tablets in ALU-PVC blister.
Secondary packing: 1 Blister is packed in an inner carton along with leaflet.
Tertiary packing: Such 10 inner cartons are packed in an outer carton. Shrink individual outer cartons with shrinkable PVC sleeves. Such 100 Shrinks are packed in a 5 Ply corrugated box sealed with BOPP tape & strap with strapping roll.

1.3.1.6.6 Special precautions for disposal and other handling
None

1.3.1.7 Applicant / Manufacturer
Applicant

Applicant name and address	**M/s. IBU PHARMA NIGERIA LIMITED.** 1,Labiran Street, Ikenne, Ogun 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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