1.3.1 Summary of product characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Product Name : **CHAKAPAIN TABLETS**

Generic Name : **Diclofenac Sodium Tablets 50 mg**

Strength : Each Uncoated Tablet Contains:
Diclofenac Sodium BP…50 mg
Excipients….q.s.
Approved Colour Used.

Pharmaceutical Form : Uncoated Tablet

Packaging : 10 Tablets are packed in Alu-PVC Blister and such 1 Blister is packed in a printed inner carton along with pack insert.

2. QUALITY AND QUANTITATIVE COMPOSITION

Batch size: 1,00,000 Tablets

Sr. No.	Ingredients	Reference	Qty./tab (mg)	Function
DRY MIXING				
1.	Diclofenac Sodium	BP	50	ACTIVE
2.	Maize Starch	BP	515.44	Binder
3.	Sodium Starch Glycolate	BP	20	Disintegrant
4.	Colloidal Silicon Dioxide (Cresol)	BP	7	Glidant
5.	Di Calcium Phosphate	BP	269.75	Diluent
6.	Cros Carmellose Sodium	BP	5	Lubricant
7.	Maize Starch**	BP		Binder
BINDING				
8.	Maize Starch	BP	32	Binder
9.	PVP K 30	BP	1.87	Lubricant
10.	Methyl Paraben	BP	1.96	Preservative
11.	Propyl Paraben	IH	0.98	Preservative
12.	Purified Water	BP	32	Solvent
LUBRICATION				
11.	Talcum	BP	22	Glidant

12.	Magnesium Stearate	BP	10	Lunricant
13.	Sodium Starch Glycolate	BP	24	Disintegrant
14.	Cros Carmellose Sodium	BP	5	Lubricant
15.	Cross Povidone XL-10	BP	3	Disintegrant
16.	Colloidal Silicon Dioxide (Cresol)	BP	2	Glidant

Legend:

BP = British Pharmacopoeia

IP = Indian Pharmacopoeia

IH = In- House Specification

Total Weight of each tablet is 970.0 mg.

3. PHARMACEUTICAL FORM VISUAL DESCRIPTION:

Oval caplet shaped, uncoated, white coloured tablet having a break line on one side & 'CHAKAPAIN' embossed on other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS:

Diclofenac Sodium Tablet is indicated in:

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

4.2 Posology and method of administration

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

The tablets should be swallowed whole with liquid, preferably before meals, and must not be chewed or divided.

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.

Special populations Pediatric population

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

The use of Diclofenac Sodium tablets in migraine attacks has not been established in children.

Elderly

Although the pharmacokinetics of diclofenac are not impaired to any clinically relevant extentin elderly patients, non-steroidal, anti-inflammatory drugs should be used with particular caution in such patients who generally are more prone to adverse reactions. In particular it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight and the patient should be monitored for GI bleeding during NSAID therapy.

Cardiovascular and significant cardiovascular risk factors

Diclofenac is contraindicated in patients with established congestive heart failure (NYHA II- IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

Patients with congestive heart failure (NYHA-I) or significant risk factors for cardiovascular disease should be treated with diclofenac only after careful consideration. Since cardiovascular risks with diclofenac may increase with dose and duration of exposure, the lowest effectivedaily dose should be used and for the shortest duration possible.

Renal impairment

Diclofenac Sodium Tablets are contraindicated in patients with renal failure .

No specific studies have been carried out in patients with renal impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering Diclofenac Sodium Tablets to patients with mild to moderate renal impairment.

Hepatic impairment

Diclofenac Sodium Tablets is contraindicated in patients with hepatic failure.

No specific studies have been carried out in patients with hepatic impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering Diclofenac Sodium Tablets to patients with mild to moderate hepatic impairment.

Methodof administration

Tablet for oral administration.

43 Contraindications

- Hypersensitivity to the active substance or any of the excipients.
- 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).

- Last trimester of pregnancy.

- Hepatic failure.

- Renal failure.

- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

- Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contraindicated in patients in whom attacks of asthma, angioedema, urticaria or acute rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.

- This product contains soya. If you are allergic to peanut or soya, do not use this medicinal product.

4.4 Special warningsand precautions for use:

General

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

The concomitant use of diclofenac with systemic 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 (see section 4.5 Interactions with othermedicaments and other forms of interaction).

Caution is indicated in the elderly on basic medical grounds. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.

As with other non-steroidal anti-inflammatory drugs including diclofenac, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug (see section 4.8 Undesirable effects). Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to diclofenac.

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

Gastrointestinal effects:

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 GI events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving diclofenac, the drug should be withdrawn.

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(see section 4.8 Undesirable effects).The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses including diclofenac, 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 (see section 4.5 Interaction with other medicaments and other forms of interaction).

Close medical surveillance and caution should be exercised in patients with ulcerative colitis, or with Crohn's disease as these conditions 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.

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 indicatedas 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 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 majorsurgery. 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 NSAIDs, including 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 arterialthrombotic 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.

4.5 Interaction with other medicinal productsand other forms of interaction

The following interactions include those observed with diclofenac gastro-resistant tablets and/orother pharmaceutical forms of diclofenac.

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: Like other NSAIDs, 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 Sodium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum Sodium 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 ofhaemorrhage 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 non-steroidal 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.

Anti-diabetics: Clinical studies have shown that diclofenac can be given together with oral anti-diabetic agents without influencing their clinical effect. However there have been isolated reports of hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the Anti-diabetic 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.

Cyclosporine: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of cyclosporine 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 cyclosporine.

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

Quinolone anti-bacterials: Convulsions may occur due to an interaction between quinolones and NSAIDs. 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 phenytoinplasma concentrations is recommended due to an expected increase in exposure to phenytoin.

4.6 Fertility, 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 ofa 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. If diclofenac is used by a woman attempting to conceive, or during the 1st 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-hydroamniosisThe mother and the neonate, at the end of the pregnancy, to:

- Possible prolongation of bleeding time, an anti-aggregating effect which may occur even atvery 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.

Female fertility

As with other NSAIDs, 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.

4.7 Effects on ability to drive and use machines

Patients who experience visual disturbances, dizziness, vertigo, somnolence, central nervous system disturbances, drowsiness, or fatigue while taking NSAIDs should refrain from driving or operating machinery.

4.8 Undesirable / side effects

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

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 (includinghypotension 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, asepticmeningitis, 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.

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4.9 Overdose

Symptoms

There is no typical clinical picture resulting from diclofenac over dosage. Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, dizziness, disorientation, excitation, coma, drowsiness, tinnitus, fainting, occasionally convulsions. In rare cases of significant poisoning acute renal failure and liver damage are possible.

Therapeutic measure

Patients should be treated symptomatically as required.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

ATC code: M01A B05

Diclofenac Sodium tablets contain the Sodium 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 Sodium 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 being.

5.2 Pharmacokinetic properties

Absorption

Diclofenac is rapidly and completely absorbed from sugar-coated tablets. Food intake does not affect absorption.

Peak plasma concentration after one 50 mg sugar-coated tablet was 3.9 µmol/l after 20-60 minutes. The plasma concentrations show a linear relationship to the size of the dose.

Diclofenac undergoes first-pass metabolism and is extensively metabolized.

Distribution

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

Diclofenac was detected in a low concentration (100ng/ml) in breast milk in one nursing mother. The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03 mg/kg/day dose.

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 Diclofenac Sodium tablets for 8 days in daily doses of 50 mg t.d.s 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 partly 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.

5.3 Preclinical safety data:

Not available.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of Excipients

Not applicable

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C in a dry place.Protect from light.

6.5 Nature and contents of container

10 Tablets are packed in Alu-PVC Blister and such 1 Blister is packed in a printed inner carton along with pack insert

6.6 Specialprecautionsfordisposalandotherhandling

No special requirements.

7. MANUFACTURER:

WINTECH PHARMACEUTICALS LTD.

Address: Office No. 2 & 3, 3rd floor, Broadway Shopping Centre, Dr. Ambedkar Road, Dadar T.T. Mumbai- 400014, India. Tel: (+ 9122) 42123456 (100 lines).

8. DISTRIBUTED BY:

PATRICKLINGO PHARMACEUTICALS LIMITED

13, Obianwu Street, Onitsha, Nigeria