1.3.1 Summary of Product Characteristics

NAME OF THE MEDICINAL PRODUCT

Brand Name: MONSTEO

Generic Name: Diclofenac Potassium Tablets 50 mg

Composition:
Each film coated tablet contains :
Diclofenac Potassium BP….50 mg Excipients…….q.s.

Approved Colours used.

Q & Q COMPOSITION:

Sr. No.	Ingredients	Reference	Qty./tab (mg)	Function
LUBRICATION				
1.	Talcum	BP	11.00	Glidant
2.	Maize Starch	BP	36.33	Binder
3.	Sodium Starch Glycolate	BP	4.00	Disintegrant
4.	Microcrystalline Cellulose Powder - 101	BP	2.66	Lubricant
5.	Cros Carmellose Sodium	BP	0.66	Lubricant
DRY MIXING (YELLOW)				
6.	Diclofenac Potassium	BP	50.00	Active
7.	Maize Starch	BP	99.84	Binder
8.	Calcium Carbonate (Light)	BP	176.00	Binder
9.	Tartrazine Supra	IH	0.28	Colouring agent
10.	Maize Starch	BP	9.59	Binder
WET GRANULATION (YELLOW)				
11.	Maize Starch	BP	20.00	Binder
12.	Sodium Methyl Paraben	BP	0.72	Preservative
13.	Sodium Propyl Paraben	BP	0.36	Preservative

14.	PVP-K 30	BP	2.80	Lubricant
15.	Purified Water	BP	*60.00 ml	Solvent

DRY MIXING (BLUE)				
16.	Maize Starch	BP	45.33	Binder
17.	Calcium Carbonate (Light)	BP	99.60	Binder
18.	Brilliant Blue Supra	IH	0.17	Colouring agent
19.	Maize Starch	BP	4.00	Binder
WET GRANULATION (BLUE)				
20.	Maize Starch	BP	4.66	Binder
21.	Sodium Methyl Paraben	BP	0.15	Preservative
22.	Sodium Propyl Paraben	BP	0.076	Preservative
23.	Purified Water	BP	*14.66 ml	Solvent
DRY MIXING (RED)				
24.	Maize Starch	BP	29.33	Binder
25.	Calcium Carbonate (Light)	BP	59.50	Binder
26.	Erythrosine Supra	IH	0.133	Colouring agent
27.	Maize Starch	BP	2.805	Binder
WET GRANULATION (RED)				
28.	Maize Starch	BP	5.73	Binder
29.	Sodium Methyl Paraben	BP	0.20	Preservative
30.	Sodium Propyl Paraben	BP	0.10	Preservative
31.	Purified Water	BP	*17.33 ml	Solvent
DRY MIXING (WHITE)				
32.	Maize Starch	BP	16.66	Binder
33.	Calcium Carbonate (Light)	BP	29.97	Binder
34.	Maize Starch	BP	1.589	Binder
WET GRANULATION (WHITE)				
35.	Maize Starch	BP	3.20	Binder

36.	Sodium Methyl Paraben	BP	0.106	Preservative
37.	Sodium Propyl Paraben	BP	0.053	Preservative
38.	Purified Water	BP	*10.66 ml	Solvent
COATING				
39.	HPMC 15 Cps	IH	2.00	Adhesive for coating
40.	Iso Propyl Alcohol	BP	*42.20	Solubilizing agent
41.	DRCOAT Glow White	IH	0.50	Colouring agent
42.	Methylene Dichloride	BP	**41.80	Solubilizing agent
	TOTAL WEIGHT		**720.10 mg**	
Total Weight/Film coated Tablet (mg) = 720.10 mg				

Legend:

BP = British Pharmacopoeia

IP = Indian Pharmacopoeia

IH = In- House Specification

USP = United States Pharmacopoeia

*Isopropyl Alcohol and Purified water are used as a solvent which is evaporated during the process and do not exist in the final formulation.

**Methylene Dichloride is used as a solvent which is evaporated during the process and do not exist in the final formulation. Total Weight of each tablet is 720.10 mg.

PHARMACEUTICAL FORM

Dosage Form: Tablets
Description: Round, Biconvex, Film coated tablet having plain surface on both sides.

CLINICAL PARTICULARS

Therapeutic indications

Diclofenac Potassium Tablets 50 mg is indicated for:

- For treatment of primary dysmenorrhea
- For relief of mild to moderate pain
- For relief of the signs and symptoms of osteoarthritis
- For relief of the signs and symptoms of rheumatoid arthritis

Posology and method of administration

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

After observing the response to initial therapy with Diclofenac Potassium tablets, the dose and frequency should be adjusted to suit an individual patient's needs.

For treatment of pain or primary dysmenorrhea the recommended dosage is 50 mg t.i.d. With experience, physicians may find that in some patients an initial dose of 100 mg of Diclofenac Potassium tablets, 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 b.i.d. or t.i.d. For the relief of rheumatoid arthritis the recommended dosage is 150-200 mg/day in divided doses, 50 mg t.i.d. or q.i.d.

Contraindications

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

Special warnings and precautions for use

Cardiovascular Effects

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see WARNINGS, GI Effects).

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke.

Hypertension

NSAIDs can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including Diclofenac Potassium Tablets, should be used with caution in patients with

hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs. Diclofenac Potassium Tablets should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal (GI) Effects: Risk of GI Ulceration, Bleeding, and Perforation NSAIDs, including Diclofenac Potassium Tablets, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID

therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects

Caution should be used when initiating treatment with Diclofenac Potassium Tablets in patients with considerable dehydration. Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a non-steroidal anti-inflammatory drug may cause a dosedependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, Reference ID: 2909337 those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced Renal Disease

No information is available from controlled clinical studies regarding the use of Diclofenac Potassium Tablets in patients with advanced renal disease. Therefore, treatment with Diclofenac Potassium Tablets is not recommended in these patients with advanced renal disease. If Diclofenac Potassium Tablets therapy must be initiated, close monitoring of the patient's renal function is advisable.

Anaphylactic Reactions

As with other NSAIDs, anaphylactic reactions may occur both in patients with the aspirin triad and in patients without known sensitivity to NSAIDs or known prior exposure to Diclofenac Potassium Tablets.

Diclofenac Potassium Tablets should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other

NSAIDs. Anaphylaxis-type reactions have been reported with NSAID products, including with diclofenac products, such as Diclofenac Potassium Tablets.

Emergency help should be sought in cases where an anaphylactic reaction occurs.

Skin Reactions

NSAIDs, including Diclofenac Potassium Tablets, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Interaction with other medicinal products and other forms of interaction

Aspirin: When Diclofenac Potassium Tablets 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 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 is administered concomitantly with cyclosporine.

ACE Inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.

Furosemide: Clinical studies, as well as post-marketing observations, have shown that Diclofenac Potassium 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 (see WARNINGS, Renal Effects), 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.

CYP2C9 Inhibitors or Inducers: Diclofenac is metabolized by cytochrome P450 enzymes, predominantly by CYP2C9. Co-administration of diclofenac with CYP2C9 inhibitors (e.g. voriconazole) may enhance the exposure and toxicity of diclofenac whereas coadministration 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.

Fertility, pregnancy and lactation Pregnancy

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 non-steroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Labor and Delivery

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred.
The effects of Diclofenac Potassium Tablets on labor and delivery in pregnant women are unknown.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Diclofenac Potassium Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

As with any NSAIDs, caution should be exercised in treating the elderly (65 years and older).

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.

Undesirable effects

Blood and lymphatic system disorders:

Thrombocytopenia, leucopoenia, anaemia, agranulocytosis.

Immune system disorders:

Hypersensitivity, anaphylactic and anaphylactoid reactions, Angioneurotic oedema.

Psychiatric disorders:

Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.

Nervous system disorders:

Headache, dizziness, Somnolence, tirednessm, Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.

Eye disorders:

Visual disturbance, vision blurred, diplopia, Optic neuritis.

Ear and labyrinth disorders:

Vertigo, Tinnitus, hearing impaired.

Cardiac disorders:

Palpitations, chest pain, cardiac failure, myocardial infarction.

Vascular disorders:

Hypertension, hypotension, vasculitis.

Respiratory, thoracic and mediastinal disorders:

Asthma (including dyspnoea), Pneumonitis.

Gastrointestinal disorders:

Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia, Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer with or without bleeding or perforation.

Hepatobiliary disorders:

Transaminases increased, Hepatitis, jaundice, liver disorder, Fulminant hepatitis, hepatic necrosis, hepatic failure.

Overdose

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.

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.

Pharmacological properties

Pharmacodynamic properties

ATC CODE - D11AX18

Diclofenac Potassium Tablets 50 mg is a non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of Diclofenac Potassium Tablets, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

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%. **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 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'-methoxydiclofenac. 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 sulfation 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-hydroxy- and 3'-hydroxy-diclofenac. In patients with renal dysfunction, peak concentrations of metabolites 4'hydroxy- and 5-hydroxydiclofenac were approximately 50% and 4% of the parent compound after single oral dosing compared to 27% and 1% in normal healthy subjects.

Excretion

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.

Preclinical safety data

Not available.

Pharmaceutical particulars

Incompatibilities Not applicable.

Shelf life

36 months

Special precautions for storage

Store below 30ºC. Protect from light and moisture.

Nature and contents of container

Blister of 12 tablets packed in unit carton with a leaflet. (Blister Pack of 20 X 1 X 12 Tablets)

Special precautions for disposal and other handling No special requirements.

MARKETING AUTHORISATION NUMBERS

NAFDAC Reg. No.: B4-7320

MARKETING AUTHORISATION HOLDER PATRICKLINGO PHARMACEUTICALS LTD.

13, Obainwu Street, Onitsha, Nigeria.

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable.

DATE OF REVISION OF THE NEXT

Not applicable.