SUMMARY OF PRODUCT CHARACTERISTICS

HABIDIP FORTE TABLET

(Paracetamol, Diclofenac sodium and Chlorzoxazone Tablets)

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. NAME OF THE MEDICINAL PRODUCT

HABIDIP FORTE TABLET (Paracetamol, Diclofenac sodium and Chlorzoxazone Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains :

Paracetamol BP……..500 mg

Diclofenac sodium BP …..…..50 mg

Chlorzoxazone USP …..…….250 mg

Colour: Sunset Yellow (In House)

For a full list of excipients, see Section 6.1.

Sr. No.	Name of ingredients	Specification	Label claim	Qty per Tab (in mg)	Function
1	Paracetamol	BP	500.0	500.00	Medicaments
2	Diclofenac Sodium	BP	50.00	50.00	Medicaments
3	Chlorzoxazone	USP	250.0	250.00	Medicaments
4	Microcrystalline Cellulose	BP	-	50.00	Binder
5	Starch Maize	BP	-	105.80	Binder
6	Methyl Paraben	BP	-	1.00	Preservative
7	Propyl Paraben	BP	-	0.20	Preservative
8	P.V.P.K 30	BP	-	5.00	Binder
9	Sodium Starch Glycolate	BP	-	6.00	Disintegrant
10	Colloidal Silicon dioxide	BP	-	2.00	Glidant
11	Magnesium Stearate	BP	-	6.00	Lubricant
12	Talcum Powder	BP	-	10.00	Lubricant
13	Colour Sunset Yellow	IHs	-	2.00	Colourant
14	Sodium Lauryl Sulphate	BP	-	6.00	Surfactant
15	Cross Povidone	BP	-	6.00	Disintegrant

3. PHARMACEUTICAL form

Solid- Dosage form (Tablets)

Description: Orange coloured ,capsule shaped uncoated tablets with a break line on one side and an embossing of HABIDIP FORTE on other side of each tablet.

4. Clinical particulars

4.1 Therapeutic indications

HABIDIP FORTE TABLET are a combination medicine used for the treatment of painful muscle spasm associated with musculoskeletal conditions.

4.2 Posology and method of administration

One tablet to be taken with food, two or three times daily.

Tablets should be swallowed whole, not chewed.

Method of administration: Oral

4.3 Contraindications

HABIDIP FORTE TABLET are contraindicated in patients with the following conditions:

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

4.4 Special warnings and precautions for use

Diclofenac Sodium

HABIDIP FORTE TABLET cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of HABIDIP FORTE TABLET in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed non-infectious, painful conditions.

The use of HABIDIP FORTE TABLET with concomitant systemic NSAIDs, including COX-2 inhibitors, should be avoided, except in patients requiring low-dose acetylsalicylic acid – caution is advised in such patients along with close monitoring. Concomitant use of a systemic NSAID and another systemic NSAID may increase the frequency of gastrointestinal ulcers and bleeding.

CV Effects

CV Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to 3 years' duration have shown an increased risk of serious CV thrombotic events, MI 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 minimise 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.

MI and stroke

Hypertension

NSAIDs can lead to onset of new hypertension or worsening of pre-existing 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 HABIDIP FORTE TABLET, 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 Oedema

Fluid retention and oedema have been observed in some patients taking NSAIDs. HABIDIP FORTE TABLET should be used with caution in patients with fluid retention or heart failure.

GI Effects: Risk of GI Ulceration, Bleeding and Perforation

NSAIDs, including HABIDIP FORTE TABLET, can cause serious GIadverse 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 1 in 5 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 1 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 GI bleeding. Patients with a prior history of peptic ulcer disease and/or GI bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared with 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 minimise 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 HABIDIP FORTE TABLET 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 NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at the greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and angiotensin-converting enzyme (ACE) inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

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 HABIDIP FORTE TABLET. It 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 HABIDIP FORTE TABLET. Emergency help should be sought in cases where an anaphylactic reaction occurs.

Skin Reactions

NSAIDs, including diclofenac sodium, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis, 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.

Haematological Effects

Anaemia is sometimes seen in patients receiving NSAIDs, including HABIDIP FORTE TABLET. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including HABIDIP FORTE TABLET, should have their haemoglobin or haematocrit checked if they exhibit any signs or symptoms of anaemia.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving HABIDIP FORTE TABLET who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Paracetamol

Use in Special Populations

Paediatric Patients

Not recommended for children under 10 years of age.

Patients with Renal/Hepatic Impairment

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with alcoholic liver disease.

Chlorzoxazone

Serious (including fatal) hepatocellular toxicity has been reported rarely in patients receiving chlorzoxazone. The mechanism is unknown but appears to be idiosyncratic and unpredictable. Factors predisposing patients to this rare event are not known. Patients should be instructed to report early signs and/or symptoms of hepatoxicity such as fever, rash, anorexia, nausea, vomiting, fatigue, right upper quadrant pain, dark urine, or jaundice. HABIDIP FORTE TABLET should be discontinued immediately and a physician consulted if any of these signs or symptoms develop. HABIDIP FORTE TABLET use should also be discontinued if a patient develops abnormal liver enzymes (e.g., AST, ALT, alkaline phosphatase and bilirubin).

The concomitant use of alcohol or other central nervous system depressants may have an additive effect.

If sensitivity reaction occurs such as urticaria, redness, or itching of the skin, the drug should be stopped.

If any symptoms suggestive of liver dysfunction are observed, the drug should be discontinued.

4.5 Interaction with other medicinal products and other forms of interaction

Diclofenac Sodium

Aspirin: When diclofenac is administered with aspirin, its protein-binding is reduced. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of diclofenac and aspirin is not generally recommended because of the potential of increased adverse effects.

Methotrexate: NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Cyclosporine: Diclofenac, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Therefore, concomitant therapy with diclofenac may increase cyclosporine's nephrotoxicity. Caution should be used when HABIDIP FORTE TABLET 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 can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure, as well as to assure diuretic efficacy.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity. Steady-state plasma lithium and digoxin levels may be increased and ketoconazole levels may be decreased.

Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

CYP2C9 Inhibitors or Inducers: Diclofenac is metabolised by cytochrome (CY) P450 enzymes, predominantly by CYP2C9. Co-administration of diclofenac with CYP2C9 inhibitors (e.g. voriconazole) may enhance the exposure and toxicity of diclofenac whereas co-administration with CYP2C9 inducers (e.g. rifampin) may lead to compromised efficacy of diclofenac. Use caution when dosing diclofenac with CYP2C9 inhibitors or inducers; a dosage adjustment may be warranted.

Other Interactions

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

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

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

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

In patients with impaired renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of an ACE inhibitor or an AIIA and/or diuretics with a cyclo-oxygenase inhibitor can increase the deterioration of the renal function, including the possibility of acute renal failure, which is usually reversible.

Antacids may delay the absorption of diclofenac. Magnesium-containing antacids have been shown to exacerbate misoprostol-associated diarrhoea.

Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

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

Voriconazole increased C_{max} and AUC of diclofenac (50 mg single dose) by 114% and 78%, respectively.

Paracetamol

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone. However, concurrent use need not be avoided.

The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, cholestyramine should not be taken within 1 hour if maximal analgesia is required.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

Restriction or avoidance of concomitant regular paracetamol use should be followed with imatinib.

Chloramphenicol plasma concentration is increased when given with paracetamol.

4.6 Pregnancy and lactation

Diclofenac Sodium

Teratogenic Effects: Pregnancy Category C

Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.

Non-Teratogenic Effects: Because of the known effects of NSAIDs on the foetal CV system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Paracetamol

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of their doctor regarding its use.

A large amount of data on pregnant women indicate neither malformative, nor foeto-/neonatal toxicity. Paracetamol can be used during pregnancy if clinically needed; however, it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

In late pregnancy, as with other NSAIDs, HABIDIP FORTE TABLET should be avoided because they may cause premature closure of the ductus arteriosus.

Chlorzoxazone

Use of Chlorzoxazone has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgement of the physician, the potential benefits outweigh the possible risks.

Labour 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 on labour and delivery in pregnant women are unknown.

Lactating Women

It is not known whether diclofenac is excreted in human milk. Paracetamol is excreted in breast milk but not in clinically significant amount. Available published data do not contraindicate breastfeeding. It is not known if chlorzoxazone is distributed into breast milk; however, the molecular weight of the drug is low

enough that excretion into breast milk is likely.

The effects of chlorzoxazone on a nursing infant are unknown.

Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from HABIDIP FORTE TABLET, 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.

Paediatric Patients

Safety and effectiveness in paediatric patients have not been established.

Geriatric Patients

As with any NSAIDs, caution should be exercised in treating the elderly (65 years of age and older). Use chlorzoxazone with extreme caution in geriatric patients due to CNS depression, potentially irreversible hepatotoxicity, or other side effects. Initially, it may be advisable to start with lower dosages in the older adult.

4.7 Effects on ability to drive and use machines

CNS depressant effects of chlorzoxazone may impair driving or operating machinery or the ability to perform other hazardous activities. Patients who experience dizziness or other central nervous system disturbances while taking NSAIDs should refrain from driving or operating machinery.

4.8 Undesirable effects

Diclofenac Sodium

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

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

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

Additional adverse experiences reported occasionally include the following:

Body as a Whole: fever, infection, sepsis

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

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

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

Metabolic and Nutritional: weight changes

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

Respiratory System: asthma, dyspnoea

Skin and Appendages: alopecia, photosensitivity, sweating increased

Special Senses: blurred vision

Urogenital System: cystitis, dysuria, haematuria, interstitial nephritis, oliguria/polyuria, proteinuria, renal failure Other adverse reactions, which occur rarely, are as follows:

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

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

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

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

Metabolic and Nutritional: hyperglycaemia

Nervous System: convulsions, coma, hallucinations, meningitis

Respiratory System: respiratory depression, pneumonia

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

Special Senses: conjunctivitis, hearing impairment.

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

Paracetamol

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

Immune System Disorders

Hypersensitivity, including skin rash, may occur

Not Known: anaphylactic shock, angio-oedema

Blood and Lymphatic System Disorders

Not Known: blood dyscrasias, including thrombocytopaenia and agranulocytosis

Skin and Subcutaneous Disorders

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

Chlorzoxazone

Chlorzoxazone-containing products are usually well tolerated. It is possible in rare instances that chlorzoxazone may have been associated with gastrointestinal bleeding. Drowsiness, dizziness, lightheadedness, malaise, or overstimulation may be noted by an occasional patient. Rarely, allergic-type skin rashes, petechiae, or ecchymoses may develop during treatment. Angioneurotic edema or anaphylactic reactions are extremely rare. There is no evidence that the drug will cause renal damage. Rarely, a patient may note discoloration of the urine resulting from a phenolic metabolite of chlorzoxazone. This finding is of no known clinical significance.

4.9 Overdose

Diclofenac Sodium

Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, confusion, disorientation, excitation, coma, tinnitus, fainting or convulsions, vomiting, headache, dizziness and epigastric pain, which are generally reversible with supportive care. GI complaints, including GI

bleeding, can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

In the case of significant poisoning, acute renal failure and liver damage are possible.

Patients should be managed by symptomatic and supportive care following a NSAID overdose. There are no specific antidotes. Emesis and/or activated charcoal (60–100 g in adults, 1–2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5–10 times the usual dose). Forced diuresis, alkalinisation of urine, haemodialysis or haemoperfusion may not be useful due to high protein-binding.

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

Paracetamol

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

Chlorzoxazone

Symptoms: Initially, gastrointestinal disturbances such as nausea, vomiting, or diarrhea together with drowsiness, dizziness, light headedness or headache may occur. Early in the course there may be malaise or sluggishness followed by marked loss of muscle tone, making voluntary movement impossible. The deep tendon reflexes may be decreased or absent. The sensorium remains intact, and there is no peripheral loss of sensation. Respiratory depression may occur with rapid, irregular respiration and intercostals and substernal retraction. The blood pressure is lowered, but shock has not been observed.

Treatment: Gastric lavage or induction of emesis should be carried out, followed by administration of activated charcoal. Thereafter, treatment is entirely supportive. If respirations are depressed, oxygen and artificial respiration should be employed and a patent airway assured by use of an oropharyngeal airway or endotracheal tube. Hypotension may be counteracted by use of dextran, plasma, concentrated albumin or a vasopressor agent such as norepinephrine. Cholinergic drugs or analeptic drugs are of no value and should not be used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

HABIDIP FORTE TABLET contain diclofenac sodium, paracetamol and chlorzoxazone. Diclofenac sodium is a NSAID (non-steroidal anti-inflammatory drug) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of diclofenac sodium, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

Paracetamol has analgesic and antipyretic actions. Chlorzoxazone is a centrally acting skeletal muscle relaxant It inhibits polysynaptic reflex arcs on the spinal cord and subcortical areas of the brain, thereby reducing skeletal muscle spasm with increased mobility of the muscle and relief of pain.

Diclofenac Sodium

Pharmacotherapeutic group (ATC code): M01AB55

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

Paracetamol

ATC code: N02B E01, Other analgesics and antipyretics

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

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

Antipyretic: Paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat-regulation centre to produce peripheral vasodilation, resulting in increased blood flow through the skin, sweating and heat loss. The central action probably involves inhibition of prostaglandin synthesis in the hypothalamus. The drug has no effect on the CV and respiratory systems and unlike salicylates, it does not cause gastric irritation or bleeding.

Paracetamol has analgesic and antipyretic actions but it has no useful anti-inflammatory properties.

Chlorzoxazone

Muscle Relaxants

Chlorzoxazone is a centrally-acting agent for painful musculoskeletal conditions. Data available from animal experiments as well as human study indicate that chlorzoxazone acts primarily at the level of the spinal cord and subcortical areas of the brain where it inhibits multisynaptic reflex arcs involved in producing and maintaining skeletal muscle spasm of varied etiology. The clinical result is a reduction of the skeletal muscle spasm with relief of pain and increased mobility of the involved muscles.

5.2 Pharmacokinetic properties

Diclofenac Sodium

Absorption

Diclofenac is 100% absorbed after oral administration compared to intravenous (IV) administration as measured by urine recovery. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available. Food has no significant effect on the extent of diclofenac absorption. However, there is usually a delay in the onset of absorption of 1–4.5 hours and a reduction in peak plasma levels of <20%.

Distribution

The apparent volume of distribution (V/F) of diclofenac sodium is 1.4 L/kg.

Diclofenac is more than 99% bound to human serum proteins, primarily to albumin. Serum protein-

binding is constant over the concentration range (0.15–105 μg/mL) achieved with recommended doses.
Diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.

Metabolism

Five diclofenac metabolites have been identified in human plasma and urine. The metabolites include 4'-hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3' hydroxy-4'-methoxy-diclofenac. The major diclofenac metabolite, 4'-hydroxy-diclofenac, has very weak pharmacologic activity. The formation of 4'-hydroxy- diclofenac is primarily mediated by CPY2C9. Both diclofenac and its oxidative metabolites undergo glucuronidation or sulphation followed by biliary excretion. Acylglucuronidation mediated by UGT2B7 and oxidation mediated by CPY2C8 may also play a role in diclofenac metabolism. CYP3A4 is responsible for the formation of minor metabolites, 5-hydroxyand 3'-hydroxy-diclofenac. In patients with renal dysfunction, peak concentrations of the metabolites, 4'-hydroxy- and 5-hydroxy-diclofenac, were approximately 50% and 4% of the parent compound after single oral dosing compared with 27% and 1%, respectively, in normal healthy subjects.

Excretion

Diclofenac is eliminated through metabolism and subsequent urinary and biliary
excretion of the glucuronide and the sulphate conjugates of the metabolites. Little or no free unchanged diclofenac is excreted in the urine. Approximately 65% of the dose is excreted in the urine and approximately 35% in the bile as conjugates of unchanged diclofenac plus metabolites. Because renal elimination is not a significant pathway of elimination for unchanged diclofenac, dosing adjustment in patients with mild-to-moderate renal dysfunction is not necessary. The terminal half-life of unchanged diclofenac is approximately 2 hours.

Paracetamol

Paracetamol is readily absorbed from the GI tract, with peak plasma levels occurring about 30 minutes to 2 hours after ingestion.
It is metabolised in the liver (90–95%) and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted unchanged.
The elimination half-life of paracetamol varies from about 1 to 4 hours. Plasma protein-binding is negligible at usual therapeutic doses but increases with increasing concentrations.
A minor hydroxylated metabolite (N-acetyl-p-benzoquinoneimine), which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione, may accumulate following paracetamol overdosage and cause liver damage.
The time to peak plasma concentration of paracetamol is 0.5–2 hours, the time to peak effect 1–3 hours, and the duration of action is 3–4 hours.

Chlorzoxazone

Blood levels of chlorzoxazone can be detected in people during the first 30 minutes and peak levels may be reached, in the majority of the subjects, in about 1 to 2 hours after oral administration of chlorzoxazone. Chlorzoxazone is rapidly metabolized and is excreted in the urine, primarily in a conjugated form as the glucuronide. Less than one percent of a dose of chlorzoxazone is excreted unchanged in the urine in 24 hours.

5.3 Preclinical safety data

Not Applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The excipients used in the formulation of HABIDIP FORTE TABLET are mentioned as follows:

- Microcrystalline Cellulose
- Starch Maize
- Methyl Paraben
- Propyl Paraben
- P.V.P.K 30
- Sodium Starch Glycolate
- Colloidal Silicon dioxide
- Magnesium Stearate
- Talcum Powder
- Colour Sunset Yellow
- Sodium Lauryl Sulphate
- Cross Povidone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 Years

6.4 Special precautions for storage

Do not store above 30^0C. Protect from Light.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Alu-PVC Blister Pack of 10 tablets in a carton with pack insert.

6.6 Special precautions for disposal <and other handling>

<No special requirements.>

<Any unused product or waste material should be disposed of in accordance with local requirements.>

7. <APPLICANT/SUPPLIER>

Applicant:

Name : HABMAY PAHRMACY LTD

Address : P.O Box A.S 81, Asawasi-Kumasi, GHANA

Telephone Number : 03220-38998

E-mail : habmay1010@yahoo.com

Supplier:

Name : MERCURY HEALTHCARE PVT LTD

Address : 12-B, Gr. Floor, Girichhaya, Loyalka Estate,

Chowpatty Band Stand, Mumbai, 400 002.

Telephone Number : ++91-22-66172224/5

E-mail : info@mercuryhealthcare.net

Web : www.mercuryhealthcare.net

8. FDA APPLICATION NUMBER

…..NA….

9. DATE OF <REGISTRATION> / <RENEWAL OF REGISTRATION>

DATE OF REGISTRATION ----------

10. DATE OF REVISION OF THE TEXT

DATE OF REVISION ----------

Reference list

[This list provides references to relevant FDA guidelines and to relevant literature and databases, in addition to the SmPC(s) of the innovator product(s). The list is compiled by FDA.]