1.3.1

Summary Of Product Characteristics (SPC)

1.3.1 Product information for health professionals

1.3.1.1 Invented Name of the Medicinal Product

CODICO FORTE

Diclofenac Potassium & Paracetamol Tablets

1.3.1.2 Strength

Diclofenac Potassium BP……50 mg

Paracetamol BP……500 mg

1.3.1.3 Dosage Form

Oral Solid Dosage Form (Film Coated Tablet)

1.3.1.4 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Diclofenac Potassium BP……50 mg

Paracetamol BP……500 mg

Excipients…….Q.S

Colour: Quinoline Yellow WS

1.3.1.5 PHARMACEUTICAL FORM

A yellow colour round biconvex film coated tablets both side plain.

1.3.1.6 CLINICAL PARTICULARS

1.3.1.6.1Therapeutic indications

CODICO FORTE is indicated for the treatment of the following:

Diclofenac in combination with Paracetamol helps reduce headaches, body pain, period and dental pain, sports and accident injuries, rheumatism, arthritis, lumbago, bursitis and sciatica.

Management of primary dysmenorrhoea, prompt pain relief, non-articular rheumatoid conditions, rheumatoid or osteo-arthritis, cervical spondylosis, infective inflammation & dental conditions,

fever as associated with inflammation.

1.3.1.6.2 POSOLOGY AND METHOD OF ADMINISTRATION

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

For oral administration

It is recommended that the tablets be taken with fluid, preferably with or after food.

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

Paediatric population

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

The use of Diclofenac Potassium & Paracetamol Tablets in migraine attacks has not been established in children.

Elderly

Although the pharmacokinetics of diclofenac are not impaired to any clinically relevant extent in elderly patients, nonsteroidal 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 (see also precautions) 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 effective daily dose should be used and for the shortest duration possible.

Renal impairment

Diclofenac Potassium & Paracetamol 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 Potassium & Paracetamol Tabletsto patients with mild to moderate renal impairment

Hepatic impairment

Diclofenac Potassium & Paracetamol 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 Potassium & Paracetamol Tabletsto patients with mild to moderate hepatic impairment

These tablets are for oral administration.

Adults, the elderly and children 16 years or older:

Age	**500mg tablet**	**How Often**
16 years and over	One – Two	Every 3 hours when necessary to a maximum of 8 doses in 24 hours

Children:

Age	**500mg tablet dose**	**How Often**
6-8 years	Half	Every 4-6 hours when necessary to a maximum of 4 doses in 24 hours
8-10 years	Half	Every 4-6 hours when necessary to a maximum of 4 doses in 24

		hours
10-12 years	One	Every 4-6 hours when necessary to a maximum of 4 doses in 24 hours
12-15 years	One – One & half	Every 4-6 hours when necessary to a maximum of 4 doses in 24 hours

Dosage instruction:

Take every 4 to 6 hours, as required. Do not take more frequently than every 4 hours. Not more than 4 doses should be administered in any 24 hour period.

1.3.1.6.3 CONTRAINDICATIONS

4.3 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 (see section Pregnancy and lactation).
- 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 nonsteroidal anti-inflammatory drugs.
- This product contains soya. If you are allergic to peanut or soya, do not use this medicinal product.

  Hypersensitivity to paracetamol or any other ingredients.

If you are taking any other medicines that contain Paracetamol.

1.3.1.6.4 WARNING AND PRECAUTIONS

General

Undesirable effects may be minimised 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

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 nonsteroidal anti-inflammatory drugs including diclofenac, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug 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 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

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 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 NSAIDs therapy, including diclofenac, particular caution is called for in patients with impaired cardiac or renal function, history of

hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery .Monitoring of renal function is recommended as a precautionary measure when using diclofenac in such cases. Discontinuation therapy is usually followed by recovery to the pre-treatment state.

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 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 .

Sodium content

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

1.3.1.6.5 Interaction with other medicinal products and other forms of interaction

The following interactions include those observed with diclofenac gastro-resistant tablets and/or other 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 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 (see section Special warnings and precautions for use).

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, like other NSAIDs, 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 NSAIDs 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 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 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 NSAIDs 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.

Alcohol reduces liver capacity to deal with paracetamol.

Chronic use of paracetamol enhances effect of warfarin and other coumarins with increased risk of bleeding; occasional doses have no significant effect. Colestyramine reduces absorption of paracetamol. Therefore, the colestyramine should not be taken within one hour if maximal analgesia is required.

Metoclopramide and Domperidone accelerate absorption of paracetamol. However concurrent use need not be avoided

May interact with Chloramphenicol causing increased plasma levels of Chloramphenicol.

1.3.1.6.6 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. 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-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 (see section Pharmacokinetic properties).

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.

See Special warnings and precautions for use, regarding female fertility.

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol being used in the recommended dosage, but patients should follow the advice of their doctor regarding its use. Paracetamol is excreted in breast milk but not in clinically significant quantities. Available published data do not contraindicate breast- feeding.

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency

1.3.1.6.7 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

.1.3.1.6.8 UNDESIRABLE EFFECTS

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.
Reproductive system and breast disorders	
Very rare	Impotence
General disorders and administration site conditions	
Rare	Oedema

* The frequency reflects data from long-term treatment with a high dose (150 mg/day).

Clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high doses (150mg daily) and in long term treatment.

Adverse events of paracetamol from historical clinical trial data are both infrequent and from small patient exposure.

Accordingly, events reported from extensive post marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by system class. Due to limited clinical trial data, the frequency of these adverse events is not known (cannot be estimated from available data), but post marketing experience indicates that adverse reactions to paracetamol are rare and serious reactions are very rare.

Immune system disorders

Hypersensitivity including skin rash may occur.

Not known: anaphylactic shock, angioedema

Blood and lymphatic system disorders

Not known: blood dyscrasias including thrombocytopenia and agranulocytosis.

Respiratory, thoracic and mediastinal disorders

Bronchospasm*

Hepatobiliary disorders

Hepatic dysfunction

* There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

Gastrointestinal

Not known: acute pancreatitis

Skin and subcutaneous disorders

Very rare cases of serious skin reactions such as Toxic Epidermal Necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis, fixed drug eruption have been reported.

1.3.1.6.9 OVERDOSE

a) 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.

b) Therapeutic measure

Patients should be treated symptomatically as required.

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.

Other measures may be indicated by the patient's clinical condition.

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 (see below).

Risk Factors:

If the patient

a, Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

Or

b, Regularly consumes ethanol in excess of recommended amounts. Or

c, Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms:

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management:

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol; however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N- acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are employed) become irreversibly bound to liver tissue.

1.3.1.7 PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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

ATC code: M01A B05

Diclofenac Potassium & Paracetamol Tabletscontain 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 & Paracetamol Tabletshave a rapid onset of action and are therefore suitable for the treatment of acute episodes of pain and inflammation.

In migraine attacks Diclofenac Potassium & Paracetamol Tabletshave 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.

ATC code: N02BE01, Other analgesics and antipyretics

Paracetamol is an effective analgesic and antipyretic agent but has only weak anti-inflammatory properties. The mechanism of action is probably similar to that of aspirin. Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system and to a lesser extent, through a peripheral action by blocking pain-impulse generation. This inhibition appears, however to be on a selective basis.

The peripheral action may also be due to inhibition of prostaglandin synthesis or to 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

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 metabolised.

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 Potassium & Paracetamol Tabletsfor 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.

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring in 30 to 60 minutes. It is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. The elimination half-life varies from about 1-4 hours after therapeutic doses. Paracetamol is relatively uniformly distributed throughout most body fluids. Binding of the drug to plasma proteins is variable*;* 20 to 30% may be bound at the concentrations encountered during acute intoxication.

Following therapeutic doses 90 - 100% of the drug may be recovered in the urine within the first day. However, practically no paracetamol is excreted unchanged and the bulk is excreted after hepatic conjugation.

A minor hydroxylated metabolite 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.

There is no pre-clinical data of relevance to a prescriber, which is additional to that already included in other sections of the SPC.

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

Preclinical safety data

Relevant information on the safety of Diclofenac Potassium & Paracetamol Tabletsis included in other sections of the Summary of Product Characteristics.

1.3.1.8. PHARMACEUTICAL PARTICULARS

1.3.1.8.1 List of excipients

Sr. No.	Name of Ingredients	Specification
Paste Preparation		
01.	Maize Starch	BP
02.	Propyl Paraben	BP
0.3	Methyl Paraben	BP
04.	Gelatin	BP
05.	PVPK 30	BP
06.	Purified Water	BP
Lubrication		
07	**Talcum**	BP
08	Sodium Lauryl Sulphate	BP
09	Colloidal Silicon Dioxide (Light)	BP
10	Cross Carmellose Sodium (Vivosol)	
Coating		
11	Aquadry Yellow	IH

1.3.1.8.2 Incompatibilities:

None stated.

1.3.1.8.3 Shelf life:

3 Years

1.3.1.8.4 Special precautions for storage:

Store below 30°C.Protect from Light.

1.3.1.8.5 Nature and contents of container:

20 x 1 x 12 Pack

20 x 1 X 12 Alu-PVC Blister packed in unit printed duplex board carton along with its package insert

1.3.1.8.6 Special precautions for disposal and other Special handling:

No special requirements.

1.3.1.9 Marketed by:

M/S. JONCO PHARMACEUTICAL COMPANY LTD.,
33, OGUI ROAD, ENUGU,
ENUGU STATE,
NIGERIA.

1.3.1.10 Manufactured by:

GLOBELA PHARMA PVT. LTD.
Plot no 357, Road No 3, GIDC,
Sachin, Surat, Gujarat,
India-394230