Diclofenac, Acetaminophen & Chlorzoxazone Tablets

Summary of Product Characteristics

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1 NAME OF THE MEDICINAL PRODUCT

Diclofenac, Acetaminophen & Chlorzoxazone Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains

Diclofenac Potassium BP	50 mg
Acetaminophen BP	325 mg
Chlorzoxazone USP	250 mg
Excipients	Q.S.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORMS

Tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic Indication.

SUPERGESIC TABLETS is used in the symptomatic management of pain and fever.

SUPERGESIC TABLETS is a preparation to manage pains & inflammation, muscle spasm prevent any muscle pain, sluggishness, fever.

4.2 Posology and method of administration.

Pain and inflammation associated with musculoskeletal and joint disorders Adult: Per tablet contains diclofenac sodium 50 mg, Acetaminophen 500 mg & Chlorzoxazone 250mg. 1 tablet trice a day.

4.3 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 (see section 4.4).

• History of gastro-intestinal bleeding or perforation, relating to previous NSAID therapy.

• During the last trimester of pregnancy (see section 4.6).

4.4 Special warnings and precaution for use.

Acetaminophen:

Where analgesics are used long-term (>3 months) with administration every two days or more frequently, headache may develop or worsen. Headache induced by overuse of analgesics (MOH medication-overuse headache) should not be treated by dose increase. In such cases, the use of analgesics should be discontinued in consultation with the doctor.

Care is advised in the administration of Acetaminophen to patients with alcohol dependency (see section 4.9), severe renal or severe hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

Label Warnings:

Do not exceed the recommended dose

If symptoms persist consult your doctor

Keep out of the reach and sight of children

Do not take with any other Acetaminophen-containing products.

Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage.

or if leaflet present:

Immediate medical advice should be sought in the event of an overdose, even if you feel well.

Diclofenac:

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).
The use of Diclofenac potassium with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects (see section 4.5).
Elderly
Caution is indicated in the elderly on basic medical grounds. The elderly have increased frequency of adverse reactions to NSAIDs especially gastro intestinal bleeding and perforation which may be fatal. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight (see section 4.2).
Gastrointestinal
Close medical surveillance is imperative in patients with symptoms indicative of gastrointestinal disorders, with a history suggestive of gastric or intestinal ulceration, bleeding or perforation, with ulcerative colitis, or with Crohn's disease as these conditions may be exacerbated (see section 4.8).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.
GI bleeding (haematemesis, melaena), ulceration or perforation, which can be fatal, has been reported with all NSAIDs 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.
The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence and maintain treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).
Caution should be advised in patients receiving concomitant medications which increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).
When GI bleeding or ulceration occurs in patients receiving diclofenac potassium, the treatment should be withdrawn.
NSAID
Hypersensitivity reactions
As with other non-steroidal anti-inflammatory drugs, allergic reactions, including anaphylactic/anaphylactoid reactions, can occur without earlier exposure to the drug (see section 4.8).
Infection
Like other NSAIDs, Diclofenac Potassium tablets may mask the signs and symptoms of infection due to their pharmacodynamic properties.
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 (see section 4.8).
Cardiovascular, Renal and Hepatic Impairment:
The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure.
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 (see section 4.3). 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.
Hepatic
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 Potassium tablets should be discontinued.

Hepatitis may occur without prodromal symptoms.
Use of Diclofenac Potassium tablets in patients with hepatic porphyria may trigger an attack.
Haematological
Diclofenac Potassium tablets may reversibly inhibit platelet aggregation (see section 4.5). Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.
Long term treatment
All patients who are receiving long term treatment with non-steroidal, anti-inflammatory agents should be monitored as a precautionary measure eg renal function, hepatic function (elevation of liver enzymes may occur) and blood counts. This is particularly important in the elderly.
Respiratory disorders
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.
Cardiovascular and cerebrovascular effects
Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy including diclofenac.
Clinical trial and epidemiological data suggest that use of diclofenac, particularly at high dose (150mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).
Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease and with significant risk factors for cardiovascular events (e.g.,, 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.
Dermatological
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 (see section 4.8). Patients appear to be at highest risk for 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 potassium should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
Impaired female fertility
The use of Diclofenac Potassium tablets 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 Potassium tablets should be considered (see section 4.6).

4.5 Interaction with other medicinal product and other forms of interaction.

Acetaminophen:

• Anticoagulants - the effect of warfarin and other coumarins may be enhanced by prolonged regular use of Acetaminophen with increased risk of bleeding. Occasional doses have no significant effect.

• Metoclopramide – may increase speed of absorption of Acetaminophen.

• Domperidone – may increase speed of absorption of Acetaminophen.

• Colestyramine – may reduce absorption if given within one hour of Acetaminophen.

• Imatinib - restriction or avoidance of concomitant regular Acetaminophen use should be taken with imatinib

Diclofenac:

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 4.4).

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.(see section 4.4)

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Lithium: If used concomitantly, diclofenac may increase plasma concentrations of lithium Monitoring of the serum lithium level is recommended.

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.

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

Anti-coagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding (see section 4.4). 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 (see section 4.4). 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.NSAID

Digoxin: If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

Selective serotonin reuptake inhibitors (SSRls): lncreased risk of gastrointestinal bleeding (see section 4.4).

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.

Zidovudine: lncreased 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.

Antidiabetic agents: Clinical studies have shown that Diclofenac Potassium tablets can be given together with oral antidiabetic agents without influencing their clinical effect. However there have been isolated reports of hypoglycaemic and hyperglycaemic effects which have required adjustment to the dosage of hypoglycaemic agents. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

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 (see section 4.4).

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.

4.6 Pregnancy and Lactation.

Acetaminophen:

Pregnancy

Epidemiological studies in human pregnancy have shown no effects due to Acetaminophen used in the recommended dosage. However, Acetaminophen should be avoided in pregnancy unless considered essential by the physician.

Breast-feeding

Acetaminophen is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

Diclofenac Potassium:

Pregnancy
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and or cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1% up to approximately 1.5%.
The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has shown to result in increased pre-and post-implantation loss and embryo-foetal lethality.
In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during organogenetic period.
NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus. If diclofenac is used by a woman attempting to conceive, or during the 1^{st} or 2^{nd} 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 5.2).

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 section 4.4 regarding female fertility.

4.7 Effect on the ability to drive and use machine.

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effect.

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.
Unknown	Neutropenia
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	
Very rare	Palpitations, chest pain, cardiac failure, myocardial infarction.
Vascular disorders	
Very rare	Hypertension, hypotension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Rare	Asthma (including dyspnoea).
Very rare	Pneumonitis.
Gastrointestinal disorders	
Common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.
Rare	Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer with or without bleeding or perforation (sometimes fatal particularly in the elderly).
Very rare	Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis.
Unknown	Ischaemic colitis
Hepatobiliary disorders	
Common	Transaminases increased.
Rare	Hepatitis, jaundice, liver disorder.
Very rare	Fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders	
Common	Rash.
Rare	Urticaria.
Very rare	Bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus.
Renal and urinary disorders	
Very rare	Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.
General disorders and administration site conditions	
Rare	Oedema
Reproductive system and breast disorders	
Very rare	Impotence

* especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus, mixed connective tissue disease, with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation.

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 dose (150mg daily) and in long term treatment. (See section 4.3 and 4.4 for).

4.9 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties.

Acetaminophen:

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

Acetaminophen's effects are thought to be related to inhibition of prostaglandin synthesis.

Diclofenac Potassium:

Diclofenac Potassium tablets contain the potassium salt of diclofenac, a non-steroidal compound with pronounced and clinically demonstrable analgesic, anti-inflammatory and anti-pyretic properties.

Diclofenac is a potent inhibitor of prostaglandin biosynthesis and a modulator of arachidonic acid release and uptake.

Diclofenac Potassium tablets have a rapid onset of action and are therefore suitable for the treatment of acute episodes of pain and inflammation.

In migraine attacks Diclofenac Potassium tablets have been shown to be effective in relieving the headache and in improving the accompanying symptom of nausea.

Diclofenac *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings.

Chlorzoxazone:

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. 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.

5.2 Pharmacokinetic properties.

Acetaminophen:

Absorption

Acetaminophen is readily absorbed from the gastrointestinal tract.

Distrubution

Peak plasma concentrations occur about 10 to 60 minutes after oral doses. Acetaminophen is distributed into most body tissues. It crosses the placenta and is present in breast milk. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

Biotransformation

It is metabolised in the liver. 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 Acetaminophen overdosage and cause tissue damage.

Elimination

It is excreted in the urine, mainly as the glucuronide and sulfate conjugates. The elimination half-life varies from about 1 to 4 hours.

Diclofenac Potassium:

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 (see section 4.6).

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 tablets for 8 days in daily doses of 50 mg t.d.s does not lead to accumulation of diclofenac in the plasma.

Approx. 60% of the dose administered is excreted in the urine in the form of metabolites, and less than 1% as unchanged substance. The remainder of the dose is eliminated as metabolites through the bile in the faeces.

Biotransformation

The biotransformation of diclofenac involves partly glucuronidation of the intact molecule but mainly single and multiple hydroxylation followed by glucuronidation.

Characteristics in patients

The age of the patient has no influence on the absorption, metabolism, or excretion of diclofenac.

In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of <10 ml/min the theoretical steady-state plasma levels of metabolites are about four times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.

In the presence of impaired hepatic function (chronic hepatitis, non-decompensated cirrhosis) the kinetics and metabolism are the same as for patients without liver disease.

Chlorzoxazone

Chlorzoxazone is administered orally. The drug is well distributed, with the highest concentrations found in plasma and fat, and lower concentrations found in the liver, muscle, brain and kidneys. The volume of distribution is roughly 14 L. It is not known if the drug is distributed into human milk or crosses the placenta. Metabolism occurs in the liver by CYP2E1, producing an inactive metabolite, 6-hydroxychlorzoxazone, which is then rapidly excreted as the glucuronide in the urine. Less than 1% of a dose is excreted unchanged in urine within 24 hours; 74% of the metabolite is excreted within 10 hours. The half-life of chlorzoxazone is roughly 60 minutes in adults with normal hepatic function.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1.	Lactose Monohydrate	BP
2.	Microcrystalline Cellulose	BP
3.	Sodium Lauryl Sulphate	BP
4.	Sodium Starch Glycolate	BP
5.	Povidone	BP
6.	Tartrazine Yellow	In House
7.	Purified Water	BP
8.	Magnesium Stearate	BP
9.	Purified Talc	BP
10.	Croscarmellose Sodium	BP

6.2 Incompatibilities
unknown

6.3 Shelf-life
36 months

6.4 Special precautions for storage
Do not store above 30°C. Store in a dry place.

6.5 Nature and composition of immediate packaging

10 tablets to packed in a blister made up of rigid non toxic PVC and printed aluminum foil. Such 10 blister are packed in a carton along with a leaflet.

6.6 Special precautions for the disposal of unused medicinal products or waste materials
None.

7 MARKETING AUTHORISATION HOLDER

8 MARKETING AUTHORISATION NUMBER(S)

9 AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

20th Feb 2024