

CIP-ZOX Tablets (Diclofenac sodium + Chlorzoxazone + Paracetamol)

Black Box Warning

Cardiovascular Risk

- Non-steroidal anti-inflammatory drugs (NSAIDs) may cause an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction and stroke, which can be fatal. This risk may increase with duration of use. Patients with CV disease or risk factors for CV disease may be at greater risk.
- Diclofenac sodium tablets are contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events, including inflammation, bleeding, ulceration and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious GI events.

Qualitative and Quantitative Composition

Each tablet contains:

Diclofenac Sodium IP.....	50 mg
Paracetamol IP.....	325 mg
Chlorzoxazone USP.....	500 mg

Dosage Form and Strength

Diclofenac Sodium 50 mg, Paracetamol 325 mg and Chlorzoxazone 500 mg oral tablets

Clinical Particulars

Therapeutic Indications

CIP-ZOX Tablets are a combination medicine used for the treatment of painful muscle spasm associated with musculoskeletal conditions.

Posology and Method of Administration

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

Tablets should be swallowed whole, not chewed.

Contraindications

CIP-ZOX Tablets 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

Special Warnings and Precautions for Use

Diclofenac Sodium

CIP-ZOX Tablets 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 **CIP-ZOX Tablets** 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 **CIP-ZOX Tablets** 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.

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

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 **CIP-ZOX Tablets**, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Oedema

Fluid retention and oedema have been observed in some patients taking NSAIDs. **CIP-ZOX Tablets** should be used with caution in patients with fluid retention or heart failure.

GI Effects: Risk of GI Ulceration, Bleeding and Perforation

NSAIDs, including **CIP-ZOX Tablets**, can cause serious GI adverse events, including inflammation, bleeding, ulceration and perforation of the stomach, small intestine or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only 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 **CIP-ZOX Tablets** in patients with considerable dehydration.

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a 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.

Advanced Renal Disease

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

Hepatic Effects

Elevations of one or more liver tests may occur during therapy with **CIP-ZOX Tablets**. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations (i.e. less than 3 times the ULN [ULN = the upper limit of the normal range]) or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients. Of the markers of hepatic function, ALT (SGPT) is recommended for the monitoring of liver injury.

In clinical trials, meaningful elevations (i.e. more than 3 times the ULN) of AST (GOT) (ALT was not measured in all studies) occurred in about 2% of approximately 5,700 patients at some time during diclofenac treatment. In a large, open-label, controlled trial of 3,700 patients treated for 2-6 months, patients were monitored first at 8 weeks and 1,200 patients were monitored again at 24 weeks. Meaningful elevations of ALT and/or AST occurred in about 4% of patients and included marked elevations (i.e. more than 8 times the ULN) in about 1% of the 3,700 patients. In that open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3-8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Elevations in transaminases were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis.

Almost all meaningful elevations in transaminases were detected before patients became symptomatic. Abnormal tests occurred during the first 2 months of therapy with diclofenac in 42 of the 51 patients in all trials who developed marked transaminase elevations.

In postmarketing reports, cases of drug-induced hepatotoxicity have been reported in the first month and, in some cases, the first 2 months of therapy, but can occur at any time during treatment with diclofenac. Postmarketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation.

Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. Based on clinical trial data and postmarketing experiences, transaminases should be monitored within 4-8 weeks after initiating treatment with diclofenac. However, severe hepatic reactions can occur at any time during treatment with diclofenac.

If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, abdominal pain, diarrhoea, dark urine, etc.), **CIP-ZOX Tablets** should be discontinued immediately.

To minimise the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (e.g. nausea, fatigue, lethargy, diarrhoea, pruritus, jaundice, right upper quadrant tenderness, and 'flu-like' symptoms), and the appropriate action patients should take if these signs and symptoms appear.

To minimise the potential risk for an adverse liver related event in patients treated with **CIP-ZOX Tablets**, the lowest effective dose should be used for the shortest duration possible. Caution should be exercised in prescribing **CIP-ZOX Tablets** with concomitant drugs that are known to be potentially hepatotoxic (e.g. antibiotics, anti-epileptics).

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 **CIP-ZOX Tablets**. 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 **CIP-ZOX Tablets**. 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 **CIP-ZOX Tablets**. 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 **CIP-ZOX Tablets**, 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 **CIP-ZOX Tablets** who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Pre-Existing Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross-reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, **CIP-ZOX Tablets** should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. In patients on longterm treatment with NSAIDs, including **CIP-ZOX Tablets**, the CBC and a chemistry profile (including transaminase levels) should be checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, **CIP-ZOX Tablets** should be discontinued.

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.

Keep out of the sight and reach of children.

Do not take paracetamol for more than 3 days without consulting a doctor.

Patients should be advised that paracetamol may cause severe skin reactions. If a skin reaction such as reddening, blisters or rash occurs, they should stop its use and seek medical assistance right away.

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 hepatotoxicity such as fever, rash, anorexia, nausea, vomiting, fatigue, right upper quadrant pain, dark urine, or jaundice. **CIP-ZOX Tablet** should be discontinued immediately and a physician consulted if any of these signs or symptoms develop. **CIP-ZOX 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.

Drug Interactions

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 **CIP-ZOX Tablets** 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 **colestyramine**. Therefore, colestyramine 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.

Use in Special Populations

Pregnant Women

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, **CIP-ZOX Tablets** 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 **CIP-ZOX Tablets**, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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.

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.

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, thrombocytopenia

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, pancytopenia

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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.

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipila.com. You can also report side effects directly via the National Pharmacovigilance Programme of India (PvPI) by calling on 1800 267 7779 (Cipla number) or you can report to PvPI on 1800 180 3024. By reporting side effects, you can help provide more information on the safety of this product.

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 haemoperfusion 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.

Pharmacological Properties

Mechanism of Action

CIP-ZOX Tablets 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.

Pharmacodynamic Properties

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.

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 CYP2C9. Both diclofenac and its oxidative metabolites undergo glucuronidation or sulphation followed by biliary excretion. Acylglucuronidation mediated by UGT2B7 and oxidation mediated by CYP2C8 may also play a role in diclofenac metabolism. CYP3A4 is responsible for the formation of minor metabolites, 5-hydroxy- and 3'-hydroxy-diclofenac. In patients with renal dysfunction, peak concentrations of 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 overdose 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.

Non-Clinical Properties

Animal Toxicology or Pharmacology

Data not available.

Description

CIP-ZOX Tablets contain diclofenac sodium, paracetamol and Chlorzoxazone. Diclofenac sodium is a NSAID) 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.

Pharmaceutical Particulars

Incompatibilities

Not applicable.

Shelf-Life

As on the pack.

Packaging Information

CIP-ZOX Tablets..... Pack of 6 tablets

Storage and Handling Instructions

Store protected from light and moisture at a temperature not exceeding 30°C

Patient Counselling Information

• What is CIP-ZOX Tablets?

CIP-ZOX Tablets contain diclofenac sodium belongs to a group of medicinal products called NSAIDs (non-steroidal anti-inflammatory drugs). paracetamol, which has analgesic and antipyretic actions and chlorzoxazone act as muscle relaxant. **CIP-ZOX Tablets** are a combination medicine used for the treatment of painful muscle spasm associated with musculoskeletal conditions.

- **Do not take if you have an allergy to this drug**

Do not take **CIP-ZOX Tablets** if you are hypersensitive to diclofenac sodium or/and other NSAIDs or/and to paracetamol or/and chlorzoxazone or/and any of the other ingredients of this medicine.

- **Before you take CIP-ZOX Tablets, tell your HCP about other medication.**

Some medicines can affect the way other medicines work. Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including the following:

- Aspirin (acetylsalicylic acid) or other NSAIDs (e.g. ibuprofen)
- Medicines used to treat osteoarthritis or rheumatoid arthritis known as cyclo-oxygenase-2 (COX2) inhibitors
- Diuretics (used to treat excess fluid in the body)
- Cyclosporine or tacrolimus (used for immune system suppression, e.g. after transplants)
- Lithium (used to treat some types of depression)
- Digoxin (a medicine for an irregular heart beat and/or heart failure)
- Warfarin or other oral anticoagulants (blood-thinning agents that reduce blood clotting, e.g. aspirin)
- Medicines used to treat anxiety and depression known as selective serotonin-re-uptake inhibitors (SSRIs)
- Medicines used to control your blood sugar (oral hypoglycaemics for diabetes)
- Methotrexate (used to treat rheumatoid arthritis, psoriasis and leukaemia)
- Steroid medications (e.g. corticosteroids, which are often used as anti-inflammatory medicines)
- Medicines for high blood pressure (anti-hypertensives)
- Magnesium containing antacids (used to treat heartburn, indigestion)
- Quinolone antibiotics (used to treat some infections)
- Ketoconazole, fluconazole, miconazole and voriconazole (used to treat some fungal infections)
- Amiodarone (used to treat an abnormal heart beat)
- Sulphinpyrazole (used to treat gout)
- If you have taken a medicine called mifepristone (used to terminate pregnancy) within the last 12 days, diclofenac should not be taken within 8–12 days of taking mifepristone
- Medicines for nausea or sickness, such as metoclopramide or domperidone
- Colestyramine for high cholesterol or high blood fats
- Imatinib, used to treat certain cancers
- Some antibiotics (chloramphenicol)
- Any other tablets or medicines, including any not prescribed by your doctor.

- **How should I take CIP-ZOX Tablets?**

Always use **CIP-ZOX Tablets** exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- **What are the possible side effects?**

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with **CIP-ZOX Tablets**. If any of the following happen, stop taking this medicine and tell your doctor immediately:

- Swelling of the hands, feet, ankles, face, lips or throat, which may cause difficulty in swallowing or breathing.

- Weakness of or inability to move one side of body, slurred speech (stroke) or chest pain (heart attack) or heart failure or palpitations (awareness of your heartbeat) – the occurrence is uncommon.
- Shortness of breath – the occurrence is uncommon.
- A decrease in a type of white blood cells (these help protect the body from infection and disease) and can lead to infections with symptoms such as chills, sudden fever, sore throat or flu-like symptoms – the occurrence is uncommon.
- Severe stomach pain or any sign of bleeding or rupture in the stomach or intestines, such as passing black or bloodstained stools – the occurrence is uncommon, or vomiting blood – this occurs rarely.
- A serious skin reaction such as rash, blistering or peeling of the skin (Stevens-Johnson syndrome, exfoliative dermatitis and toxic epidermal necrolysis) – this occurs very rarely.
- A serious allergic reaction such as skin rash, swelling of the face, wheezing or difficulty breathing (anaphylactic shock) – this occurs rarely.
- Jaundice (your skin or the whites of your eyes look yellow) – this occurs rarely.
- Reduction in the number of blood platelets (increased chance of bleeding or bruising) – it is not known how often this occurs.
- Symptoms of meningitis [stiff neck, headache, nausea (feeling sick), vomiting, fever or loss of consciousness] – it is not known how often this occurs.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

Very common: may affect more than 1 in 10 people

- Stomach ache, diarrhoea, nausea (feeling sick), indigestion

Diarrhoea is the most common problem and is occasionally severe. You have less chance of getting diarrhoea if you take diclofenac with food. If you use an antacid (something to reduce acid in the stomach) you should avoid antacids with magnesium in them as these may make diarrhoea worse.

Common: may affect up to 1 in 10 people

- Rash, itching
- Vomiting, wind, constipation, burping, gastritis (indigestion, stomach ache, vomiting)
- Ulcers in the stomach or intestines
- Headache, dizziness, feeling sleepy
- Difficulty sleeping
- Changes in blood tests relating to the liver
- Inflammation of the digestive tract, including the intestines, such as nausea, diarrhoea, abdominal pain
- Abnormal formation of foetus

Uncommon: may affect up to 1 in 100 people

- Swelling of the mouth
- Fluid build-up in the body that can cause swollen ankles and legs
- Abnormal or unexpected bleeding from the vagina, menstrual disturbances
- Reduction in the number of blood platelets (increased chance of bleeding or bruising)
- Purpura (purple spots on the skin)
- Urticaria (raised itchy rash)
- Infection of the vagina (itching, burning, soreness, pain – especially during intercourse and/or

urination)

- Blurred vision
- High blood pressure
- Loss of appetite
- Menstrual disorders such as usually heavy or light bleeding, or delayed periods
- Chills or fever
- Drowsiness, tiredness, feeling shaky
- Ringing in the ears
- Depression and feeling anxious
- Tingling or pricking (pins and needles)
- Mouth ulcers and dry mouth

Rare: may affect up to 1 in 1,000 people

- Inflammation of the liver (possible yellow discolouration of the skin, headache, fever, chills, general weakness)
- Inflammation of the pancreas, which causes severe pain in the abdomen and back
- Inflammation of the lungs, such as coughing, increased sputum
- Breast pain
- Vomiting blood
- Worsening of ulcerative colitis (inflammation of the lower intestine)
- Damage to the gullet
- Swelling of the tongue
- Low blood pressure

- Hair loss
- Increased sensitivity to light
- Nightmares

Very rare: may affect up to 1 in 10,000 people

- Severe liver disorders, including liver failure

Not known: frequency cannot be estimated from the available data

- Worsening of Crohn's disease (inflammation of the intestines)
- Kidney problems
- Seizures
- Inflamed blood vessels (can cause fever, aches, purple blotches)
- Psychotic disorder (mental disorder that features loss of contact with reality)
- Mood swings, irritability, memory problems, feeling confused
- Difficulty seeing, changes in the way things taste
- Inflammation
- Abnormal contractions of the womb, rupture in the womb, retained placenta after giving birth, a life-threatening reaction in the mother due to the passage of amniotic fluid (fluid covering the foetus) or other foetal material into the maternal blood stream, bleeding in the womb, miscarriage, death of the unborn baby, premature birth
- Anaemia (low number of red blood cells) which can lead to pale skin and cause weakness or breathlessness
- Painful menstrual/period cramps
- Decreased fertility in females

- **How should I store CIP-ZOX Tablets?**

Keep this medicine out of the sight and reach of children.

Store in a dry place and protect from light.

Store in the original packaging.

Do not use this medicine after the expiry date stated on the blister pack and carton. The expiry date refers to the last day of that month.

• **General information about the safe and effective use of this drug.**

CIP-ZOX Tablets are a combination of diclofenac sodium and paracetamol and is used for the treatment of pain and inflammation associated with musculoskeletal and joint disorders and pain and cramps associated with menstruation.

Do not take this medicine if you

- have had an allergic reaction such as a skin rash, swelling or itchiness of the skin, severe nasal congestion, asthma or wheezing after taking diclofenac or other NSAIDs such as aspirin (acetylsalicylic acid);
- currently have an ulcer or perforation (hole) in your stomach or intestines;
- currently suffer from bleeding in your stomach, intestines or brain;
- are undergoing or you have just had coronary artery bypass graft (CABG) surgery;
- have severe kidney or liver failure;
- have established heart disease and/or cerebrovascular disease, e.g. if you have had a heart attack; stroke, mini-stroke (TIA) or blockages to blood vessels to the heart or brain or an operation to clear or bypass blockages;
- have or have had problems with your blood circulation (peripheral arterial disease);
- have inflammation of the intestines (ulcerative colitis or Crohn's disease);
- are dehydrated;
- are pregnant, or trying to become pregnant, because it may cause a miscarriage;
- are a woman of childbearing age and you are not using an effective contraceptive method to avoid becoming pregnant;
- are over the age of 65 years (your doctor will need to monitor you regularly); and/or,
- are taking other medicine containing paracetamol.

If you feel dizzy or drowsy after taking **CIP-ZOX Tablets**, do not drive and do not use any tools or machines until these effects have worn off.

• **What are the ingredients?**

CIP-ZOX Tablets contain diclofenac sodium 50mg, paracetamol 325mg and Chlorzoxazone 500mg.

• **Any other information**

Before you are given this medicine, make sure your doctor knows if you

- smoke;
- have diabetes; and/or,
- have angina, blood clots, high blood pressure, raised cholesterol or raised triglycerides

This medicine may be associated with a small increased risk of heart attack (myocardial

infarction) or stroke. Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose or duration of treatment.

Side effects may be minimised by using the lowest effective dose for the shortest duration necessary.

As with other NSAIDs (e.g. ibuprofen), **CIP-ZOX Tablets** may lead to an increase in blood pressure and, so, your doctor may advise you to monitor your blood pressure on a regular basis.

If you have heart, liver or kidney problems, your doctor will advise regular monitoring of the same.

Details of the Manufacturer

Mfd. By Cipla Ltd.

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Details of Permission or Licence Number with Date

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