For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

DICLOGESIC

1. Generic Name

Diclofenac Sodium and Paracetamol Tablets I.P.

2. Qualitative and quantitative composition

Each uncoated tablet contains:

Diclofenac Sodium I.P.

(As enteric coated granules) 50 mg

Paracetamol I.P…….325 mg

Excipients……q.s.

The excipients used are Microcrystalline Cellulose, Pregelatinized Starch , Ethyl Cellulose, Methyl Paraben, Propyl Paraben, Iso propyl alcohol, Methylene chloride, Sodium starch Glycollate, Microcrystalline Cellulose, Talc, Colloidal Silicon dioxide, Magnesium stearate

3. Dosage form and strength

Dosage form: Uncoated tablet

Strength: Diclofenac Sodium 50 mg and Paracetamol 325 mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for the symptomatic treatment of acute pain and inflammation in patients with osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

4.2 Posology and method of administration

Dose: As directed by the Physician.

4.3 Contraindications

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

• Active, or gastric or intestinal ulcer, bleeding or perforation.

• History of gastrointestinal bleeding or perforation, relating to previous NSAIDs 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 4.6).

• 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, urticarial or acute

rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs

4.4 Special warnings and precautions for use

Diclofenac sodium

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 sodium tablets 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 (see section 4.5).

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 (see section 4.8). 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 infection due to its pharmacodynamic properties.

This medicine contains sucrose and therefore is not recommended for patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency.

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 gastrointestinal (GI) events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving diclofenac, the medicinal product 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 (see 4.8). 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 an increased frequency of adverse reactions to NSAIDs especially gastrointestinal 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 other medicinal products likely to increase gastrointestinal risk (see below and section 4.5).

Patients with a history of GI toxicity, particularly the 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 (see section 4.5).

Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated (see section 4.8).

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 impairment

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 impairment

As fluid retention and oedema have been reported in association with NSAID 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 in those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery (see 4.3). Monitoring of renal function is recommended as a precautionary measure when using diclofenac in such cases. Discontinuation of 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 (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 sodium tablets 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 (see section 4.8).

Cardiovascular and cerebrovascular effects

Patients with congestive heart failure (NYHA-1) or patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, and 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-1) 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

During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of the blood count is recommended.

Diclofenac may reversibly inhibit platelet aggregation (see anticoagulants in section 4.5). 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,

Paracetamol

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

Do not exceed the stated dose.

Patients should be advised to consult their doctor if their headaches become persistent.

Patients should be advised not to take other paracetamol-containing products concurrently.

Patients should be advised to consult a doctor if they suffer from non-serious arthritis and need to take painkillers every day.

If symptoms persist consult your doctor.

Keep out of the reach and sight of children.

Pack Label:

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

Do not take with any other paracetamol-containing products.

Patient Information Leaflet:

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.

4.5 Drugs interactions

Diclofenac sodium

The following interactions include those observed with diclofenac gastro-resistant tablets and/or other pharmaceutical forms of diclofenac.

***Lithium*:** If used concomitantly, diclofenac may raise 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 Anti-hypertensive agents*:** Like other NSAIDs, concomitant use of diclofenac with diuretics or 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 and 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 (see section 4.4).

***Anticoagulants 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 affects the action of anticoagulants,

there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants 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 high dose can reversibly inhibit platelet aggregation.

Other NSAIDS including cyclo-oxygenase-2selective inhibitors and corticosteroids: Co-administration of diclofenac and 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).

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of SSRIs may increase the risk of gastrointestinal bleeding (see section 4.4).

***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 increased.

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 antimicrobials: 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 concentration and exposure to diclofenac due to inhibition of diclofenac metabolism**.**

Paracetamol

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Diclofenac Sodium

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 of 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 been 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 the organogenetic period. If diclofenac is used by a woman attempting to conceive, or during the first and second trimester 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 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 sodium tablets are contraindicated during the third trimester of pregnancy.

Breast-feeding:

Like other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, diclofenac should not be administered during breast feeding in order to avoid undesirable effects in the infant.

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 have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of diclofenac should be considered (see also section 4.4 regarding female fertility).

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

4.7 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 operate machinery.

4.8 Undesirable effects

Adverse reactions (Table 1) are ranked under 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, <1/1,000); very rare (<1/10,000); Not known: cannot be estimated from the available data.

The following undesirable effects include those reported with either short-term or long-term use.

Table 1

Blood and lymphatic system disorders	
Very rare	leucopoenia, anaemia (including haemolytic and aplastic anaemia),
Not Known	Thrombocytopenia,, agranulocytosis.
Immune system disorders	
Rare Very rare	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock). Angioneurotic oedema (including face oedema).
Not Known	Anaphylaxis, Cutaneous hypersensitivity reactions including skin rashes Stevens Johnson syndrome/toxic epidermal necrolysis

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.
Not Known	Bronchospasm
Gastrointestinal disorders	
Common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.

Rare Very rare Unknown	Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer with or without bleeding or perforation (sometimes fatal particularly in the elderly). 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. Ischaemic colitis
Hepatobiliary disorders	
Common Rare Very rare	Transaminases increased. Hepatitis, jaundice, liver disorder. Fulminant hepatitis, hepatic necrosis, hepatic failure.
Not known	Hepatic dysfunction
Skin and subcutaneous tissue disorders	
Common Rare Very rare	Rash. Urticaria. 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 (150mg/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 dose (150 mg daily) and in long term treatment (see sections 4.3 and 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose

Diclofenac Sodium

Symptoms

There is no typical clinical picture resulting from diclofenac over dosage. Over dosage can cause symptoms such as headache, nausea, vomiting, epigastric pain, gastrointestinal haemorrhage, diarrhoea, dizziness, disorientation, excitation, coma, drowsiness, tinnitus, fainting or convulsions. In the case of significant poisoning acute renal failure and liver damage are possible.

Therapeutic measure

Management of acute poisoning with NSAIDs, including diclofenac, essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

Special measures such as forced diuresis, dialysis or haemo-perfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism.

Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination (e.g. vomiting, gastric lavage) after ingestion of a potentially life threatening overdose.

Paracetamol

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g 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 Nacetylcysteine, 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.

5. Pharmacological properties

5.1 Mechanism of Action

Diclofenac Sodium:

Diclofenac sodium is a non-steroidal agent with marked analgesic/anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase, (cyclo-oxygenase).

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

Paracetamol

Paracetamol is an antipyretic analgesic. The mechanism of action is probably similar to that of aspirin and dependant on the inhibition of prostaglandin synthesis. This inhibition appears, however to be on a selective basis.

5.2 Pharmacodynamics properties

Diclofenac Sodium

Pharmacotherapeutic group

Non-steroidal anti-inflammatory drugs (NSAlDs).

Mechanism of action:

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Paracetamol

Paracetamol is an antipyretic analgesic. The mechanism of action is probably similar to that of aspirin and dependant on the inhibition of prostaglandin synthesis. This inhibition appears, however to be on a selective basis.

Clinical Efficacy

In a reported two dental pain studies, pain relief was observed at a median time of 15 minutes following administration of the 1000 mg dose of Paracetamol tablets (new formula).

Paracetamol tablets (new formula) demonstrated superior pain relief at 1000 mg dose compared to placebo and to Paracetamol tablets (new formula) at 500 mg dose Paracetamol tablets (new formula) at the 500 mg dose also demonstrated superior efficacy compared to placebo

5.3 Pharmacokinetic properties

Diclofenac Sodium

After ingestion of the diclofenac slow release tablet, the active principle is slowly released into the gastrointestinal contents. Once released from the tablet, diclofenac is rapidly absorbed from the gastrointestinal tract but is subject to first-pass metabolism. Peak plasma concentrations occur about 4.5 hours after administration of the prolonged release tablets when taken with a meal. Food and antacids decrease the rate but not the extent of absorption of diclofenac. The systemic availability of diclofenac from the SR formulations is on average 82% of that achieved with the same dose of enteric-coated tablets (possibly due to release rate dependent first-pass metabolism). The active substance is 99.7% bound to plasma proteins, mainly albumin.

Diclofenac enters the synovial fluid and peak synovial fluid concentrations at steady state exceed plasma concentrations. Furthermore, elimination from the synovial fluid is slower than from plasma. Diclofenac and its metabolites cross the placenta and traces of diclofenac have been found in the milk of lactating women. The half-life for the terminal elimination phase is 3 hours. Approximately 60% of the administered dose is excreted via the kidneys in the form of metabolites and less than 1% in unchanged form. About 30% of the dose is excreted via the bile in metabolised form. In patients with impaired renal function, accumulation of diclofenac sodium has not been reported. However, half-life of diclofenac may be prolonged in patients with severe renal impairment.

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 sulfation 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 metabolites 4'-hydroxy- and 5-hydroxy-Diclofenac were approximately 50% and 4% of the parent compound after single oral dosing compared to 27% and 1% in normal healthy subjects.

Paracetamol

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. The concentration in plasma reaches a peak in 30 to 60 minutes and the plasma half-life is 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.

Paracetamol contain a disintegrate system which accelerates tablet dissolution compared to standard paracetamol tablets.

Human scintigraphy data demonstrate that Paracetamol generally start to disintegrate by 5 minutes post dose in the stomach. There is also less between-subject and less within-subject variability ($p<0.0001$) in early absorption of paracetamol from Paracetamol compared to standard paracetamol tablets.

Human pharmacokinetic data demonstrate that the time taken to reach plasma paracetamol therapeutic threshold (4-7mcg/ml) is at least 37% faster with Paracetamol compared to standard paracetamol tablets ($P<0.05$).

Total extent of absorption of paracetamol from Paracetamol is equivalent to that from standard paracetamol tablets.

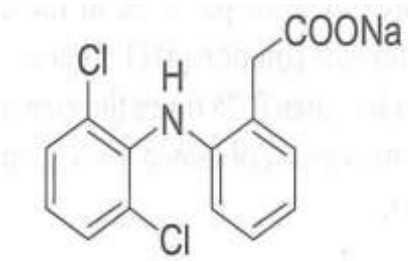
6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

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

7. Description

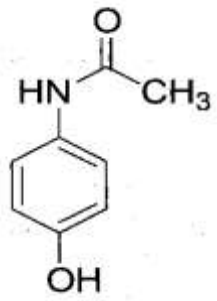
Diclofenac Sodium is sodium 2-[(2, 6-dichlorophenyl) amino]phenyl acetate. Having molecular formula of $C_{14}H_{10}CL_2NNaO_2$ and molecular weight is 318.1 the chemical structure is:



Diclofenac Sodium is a white to slightly yellowish crystalline powder;

Slightly hygroscopic. Which is freely soluble in methanol; soluble in ethanol (95 percent); sparingly soluble in water and in glacial acetic acid; practically insoluble in ether, in chloroform and in toluene.

Paracetamol is 4-hydroxyacetanilide having molecular formula of $C_8 H_9 NO_2$ and Molecular weight is 151.2. The chemical structure is:



DICLOGESIC Tablets are white to off-white, round shaped, flat faced beveled edge, uncoated tablets plain on both sides. The excipients used are Microcrystalline Cellulose, Pregelatinized Starch , Ethyl Cellulose, Methyl Paraben, Propyl Paraben, Iso propyl alcohol, Methylene chloride, Sodium starch Glycollate, Microcrystalline Cellulose, Talc, Colloidal Silicon dioxide, Magnesium stearate.

8. Pharmaceutical particulars

8.1 Incompatibilities

None Stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

Diclogesic is packed in blister strips of 10 tablets

8.4 Storage and handing instructions

Store at a temperature not exceeding 30^0c, protected from light and moisture.Keep out of reach of children.

9. Patient Counselling Information

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet?

9.5 How to store Diclogesic

9.6 Contents of the pack and other information

9.1.What Diclogesic are **and what they are used for.**

Diclogesic is combination of active ingredients Diclofenac sodium and Paracetamol which is non-steroidal anti-inflammatory drugs (NSAIDs)

Diclogesic is indicated for the symptomatic treatment of acute pain and inflammation in patients with osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

DICLOGESIC tablets are not suitable for children.

9.2 What you need to know before you use Diclogesic

Do not use Diclogesic if: (Writer CONTRAINDICATION if PIL is not available)

- You are allergic to **Diclogesic** or to any of the other ingredients of this medicine. ibuprofen or to any other NSAID, or any of the other ingredients of DICLOGESIC tablets Signs of a hypersensitivity reaction include swelling of the face and mouth (angioedema), breathing problems, chest pain, runny nose, skin rash or any other allergic type reaction.
- you have now, or have ever had, a stomach (gastric) or duodenal (peptic) ulcer, or bleeding in the digestive tract (this can include blood in vomit, bleeding when emptying bowels, fresh blood in faeces or black, tarry faeces)
- you have had stomach or bowel problems after you have taken other NSAIDs
- you have severe heart, kidney or liver failure
- You 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.
- You have or have had problems with your blood circulation (peripheral arterial disease).
- you are more than six months pregnant

Warning and Precautions

Talk to your doctor or pharmacist before taking Diclofenac if:

- you suffer from any stomach or bowel disorders including ulcerative colitis or Crohn's disease
- you have kidney or liver problems, or you are elderly
- you have a condition called porphyria
- You suffer from any blood or bleeding disorder. If you do, your doctor may ask you to go for regular checkups
- While you are taking these tablets.
- you ever had asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (nasal polyps), chronic
- Pulmonary diseases or infections of the respiratory tract.
- you are breast feeding
- you have angina, blood clots, high blood pressure, raised cholesterol or raised triglycerides

- you have heart problems or if you had a stroke or you think you might be at risk of these conditions (for
- example, if you have high blood pressure, diabetes or high cholesterol or are a smoker)
- you have diabetes
- you smoke
- you have Systemic Lupus Erythematosus SLE (inflammatory, auto-immune disorder which causes
- symptoms such as joint pain, joint inflammation, skin rashes, fever) or any similar condition
- you have an intolerance to some sugars such as sucrose (these tablets contain sucrose)

Tell your doctor if you recently had or you are going to have a surgery of the stomach or intestinal tract before taking DICLOGESIC , as DICLOGESIC can sometimes worsen wound healing in your gut after surgery.

Tell your doctor or pharmacist if you have any of these conditions because DICLOGESIC might not be the right medicine for you.

Children

DICLOGESIC tablets are not suitable for children.

Other medicines and DICLOGESIC

Some medicines can interfere with your treatment. Please tell your doctor or pharmacist if you are taking any of the following:

• Medicines to treat diabetes

• Anticoagulants (blood thinning tablets like warfarin)

• Diuretics (water tablets)

• Lithium (used to treat some mental problems)

• Methotrexate (for treatment of some inflammatory diseases and some cancers)

• Ciclosporin and tacrolimus (used to treat some inflammatory diseases and after transplants)

• Trimethoprim (a medicine used to prevent or treat urinary tract infections)

• Quinolone antibiotics (for infections)

• Any other NSAID or COX-2 (cyclo-oxygenase-2) inhibitor, for example aspirin or ibuprofen

• Mifepristone (a medicine used to terminate pregnancy)

• Cardiac glycosides (for example digoxin), used to treat heart problems

• Medicines known as SSRIs (used to treat depression)

• Oral steroids (an anti-inflammatory drug)

• Medicines used to treat heart conditions or high blood pressure, for example beta blockers or ACE inhibitors

• Voriconazole (a medicine used to treat fungal infections).

• Phenytoin (a medicine used to treat seizures)

• Colestipol/cholestyramine (used to lower cholesterol)

DICLOGESIC with food and drink

Take this medicine with or after food

Pregnancy and breast-feeding

• Although not common, abnormalities have been reported in babies whose mothers have taken NSAIDs during pregnancy. You should not take DICLOGESIC during the last 3 month of pregnancy as it may affect the baby's circulation.

• You should advise your doctor or pharmacist if you think you might be pregnant or are up to 6 month pregnant.

• Taking DICLOGESIC may make it more difficult to become pregnant. You should talk to your doctor if you are planning to become pregnant, or if you have problems getting pregnant.

• You should avoid taking DICLOGESIC whilst breast feeding.

Driving and using machines

Very occasionally people have reported that diclofenac sodium tablets have made them feel dizzy, tired or sleepy. Problems with eyesight have also been reported. If you are affected in this way, you should not drive or operate machinery.

Other special warnings

• You should take the lowest effective dose of Diclofenac Sodium for the shortest possible time particularly if you are underweight or elderly.

• There is a small increased risk of heart attack or stroke when you are taking any medicine like Diclofenac containing medicine. The risk is higher if you are taking high doses for a long time. Always follow the doctor’s instructions on how much to take and how long to take it for.

• If at any time while taking DICLOGESIC you experience any signs or symptoms of problems with your heart or blood vessels such as chest pain, shortness of breath, weakness or slurring of speech, contact your doctor immediately.

• Whilst you are taking these medicines your doctor may want to give you a check-up from time to time.

• If you have a history of stomach problems when you are taking NSAIDs, particularly if you are elderly, you must tell your doctor straight away if you notice any unusual symptoms.

• Because it is an anti-inflammatory medicine, Diclofenac Sodium tablets may reduce the symptoms of infection, for example, headache, and high temperature. If you feel unwell and need to see a doctor, remember to tell him or her that you are taking Diclofenac Sodium tablets.

9.3 How to use Diclogesic

The doctor will tell you how many DICLOGESIC tablets to take and when to take them. Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Swallow the tablets whole with a glass of water. DO NOT crush or chew the tablets as this will affect the special “slow release” system.

Dose: As directed by the Physician.

Children: These tablets are not suitable for children.

The doctor may also prescribe another drug to protect the stomach to be taken at the same time, particularly if you have had stomach problems before, or if you are elderly, or taking certain other drugs as well.

If you take more DICLOGESIC than you should

If you, or anyone else, accidentally takes too much DICLOGESIC , tell your doctor or go to your nearest hospital casualty department immediately. Take your medicine pack with you so that people can see what you have taken.

Symptoms of an overdose can include: headache, nausea (feeling sick), vomiting, abdominal pain, stomach or intestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, ringing in the ears, fainting, or occasionally convulsions (seizures, uncontrolled fits).

If you forget to take DICLOGESIC

It is important that you do not miss a dose. If you forget to take a dose, take one as soon as you remember. If it is nearly time for your next dose, just take the next dose and forget about the one you missed. DO NOT take a double dose to make up for a forgotten tablet. Do not take more than 150 mg in 24 hours. If you have trouble remembering to take the tablets, tell your doctor or pharmacist.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, these tablets can cause side effects, although not everybody gets them.

Some side effects can be serious

STOP TAKING DICLOGESIC and tell your doctor straight away if you notice:

• Sudden and crushing chest pain (signs of myocardial infarction or heart attack)

• Breathlessness, difficulty breathing when lying down, swelling of the feet or legs (signs of heart failure)

• Sudden weakness or numbness in the face, arm or leg especially on one side of the body; sudden loss or disturbance of vision; sudden difficulty in speaking or ability to understand speech; sudden migraine like headaches which happen for the first time, with or without disturbed vision. These symptoms can be an early sign of a stroke

• Stomach pain, indigestion, heartburn, wind, nausea (feeling sick) or vomiting (being sick)

• Any sign of bleeding in the stomach or intestine, for example, when emptying your bowels, blood in vomit or black, tarry faeces

• Allergic reactions which can include skin rash, itching, bruising, painful red areas, peeling or blistering

• Wheezing or shortness of breath (bronchospasm)

• Swollen, face, lips, hands or fingers

• Yellowing of your skin or the whites of your eyes

• Persistent sore throat or high temperature

• An unexpected change in the amount of urine produced and/or its appearance.

• Mild cramping and tenderness of the abdomen, starting shortly after the start of the treatment with DICLOGESIC and followed by rectal bleeding or bloody diarrhea usually within 24 hours of the onset of abdominal pain

• Stevens-Johnson syndrome (serious illnesses with blistering of the skin, mouth, eyes and genitals) If you notice that you are bruising more easily than usual or have frequent sore throats or infections, tell your doctor.

Tell your doctor immediately if you notice the following:

• Chest pain, which can be a sign of a potentially serious allergic reaction called Kounis syndrome

The side effects listed below have also been reported.

Common side effects (These may affect between 1 and 1 in 10 in every 100 patients):

• Stomach pain, heartburn, nausea, vomiting, diarrhea, indigestion, wind, loss of appetite

• Headache, dizziness, vertigo

• Skin rash or spots

• Raised levels of liver enzymes in the blood

Uncommon side effects (These may affect between 1 and 10 in every 1000 patients):

• Fast or irregular heart beat (palpitations), chest pain, heart disorders, including heart attack or breathlessness, difficulty breathing when lying down, or swelling of the feet or legs (signs of heart failure), especially if you have been taking a higher dose (150 mg per day) for a long period of time.

Rare side effects (These may affect between 1 in every 1,000 to 1 in every 10,000 patients):

• Stomach ulcers or bleeding (there have been very rare reported cases resulting in death, particularly in the elderly)

• Gastritis (inflammation, irritation or swelling of the stomach lining)

• Vomiting blood

• Diarrhoea with blood in it or bleeding from the back passage

• Black, tarry faeces or stools

• Drowsiness, tiredness

• Skin rash and itching

• Fluid retention, symptoms of which include swollen ankles

• Liver function disorders, including hepatitis and jaundice

• Asthma (symptoms may include wheezing, breathlessness, coughing and a tightness across the chest)

Very rare side effects (These may affect less than 1 in every 10,000 patients):

Effects on the nervous system:

Inflammation of the lining of the brain (meningitis), tingling or numbness in the fingers, tremor, visual disturbances such as blurred or double vision, taste changes, hearing loss or impairment, tinnitus (ringing in the ears), sleeplessness, nightmares, mood changes, depression, anxiety,

irritability, mental disorders, disorientation and loss of memory, fits, headaches together with a dislike of bright lights, fever and a stiff neck.

Effects on the stomach and digestive system:

Constipation, inflammation of the tongue, mouth ulcers, inflammation of the inside of the mouth or lips, lower gut disorders (including inflammation of the colon or worsening of ulcerative colitis or Crohn's disease), inflammation of the pancreas.

Effects on the chest or blood:

Hypertension (high blood pressure), hypotension (low blood pressure, symptoms of which may include faintness, giddiness or light headedness), inflammation of blood vessels (vasculitis), inflammation of the lung (pneumonitis), blood disorders (including anaemia).

Effects on the liver or kidneys:

Kidney or severe liver disorders including liver failure, presence of blood or protein in the urine

Effects on skin or hair:

Facial swelling, serious skin rashes including Stevens-Johnson syndrome, Lyell's syndrome and other skin rashes which may be made worse by exposure to sunlight. Hair loss

Effects on the reproductive system:

Impotence.

Other side effects that have also been reported with unknown frequency include:

Throat disorders, confusion, hallucinations, malaise (general feeling of discomfort), inflammation of the nerves in the eye, disturbances of sensation

Medicines such as diclofenac containing medicine may be associated with a small increased risk of heart attack or stroke.

Do not be alarmed by this list - most people take Diclofenac containing medicine without any problems. If any of the side effects becomes serious, or if you notice side effects not listed in this leaflet, please tell your doctor. He/she may want to give you a different medicine.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store Diclogesic

STORE AT A TEMPERATURE NOT EXCEEDING 30^0C, PROTECTED FROM LIGHT AND Moisture. Keep out of reach of children.

9.6 Contents of the pack and other information

Each uncoated tablet contains:

Diclofenac Sodium I.P. 50 mg

Paracetamol I.P.325 mg

The excipients used are Microcrystalline Cellulose, Pregelatinized Starch , Ethyl Cellulose,

Methyl Paraben, Propyl Paraben, Iso propyl alcohol, Methylene chloride, Sodium starch Glycollate, Microcrystalline Cellulose, Talc, Colloidal Silicon dioxide, Magnesium stearate

DICLOGESIC is packed in blister strips of 10 tablets

10 Details of manufacturer

TORRENT PHARMACEUTICALS LTD.

32 No. Middle Camp, NH-10,

East District, Gangtok, Sikkim-737 135

11 Details of permission or licence number with date

M/563/2010 issued on 16.09.2017

12 Date of revision

May 2020

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

Torrent House, Off Ashram Road,

Ahmedabad-380 009, INDIA

IN/ DICLOGESIC 325, 50 mg/May-20/04/PI