Diclofenac Sodium 50mg, Paracetamol 325mg and Serratiopeptidase 15 mg
ENZOFLAM

1. NAME OF THE MEDICINAL PRODUCT

ENZOFLAM

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Diclofenac sodium…….. .50 mg

Paracetamol ……. 325mg

Serratiopeptidase……...15mg (as enteric coated granules)

3. PHARMACEUTICAL FORM

Tablet for oral use.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Resolution of inflammation and pain due to bone and soft tissue injury.

Resolution of post-operative inflammation, oedema and pain.

4.2 Posology and Method of Administration

Enzoflam is supplied for oral administration in adults and should be swallowed whole with a sufficient amount of liquid. It should be taken preferably with or after food. The maximum recommended dose of Enzoflam is two tablets daily, taken as one tablet in the morning and one in the evening. The dosage for the combination should not be used than maximum dosage of individual agent.

Diclofenac

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

For oral administration 75-150mg daily in two or three divided doses.

Children (aged 1-12 years): 1-3mg/kg per day in divided doses. (25mg tablet only)

Paracetamol
Adults, the elderly and young persons over 12 years Maximum of up to 4gm daily can be given by oral route.

Children age 6 to 12 years of age Maximum of up to 2gm in 24 hours can be given.

Dose Modification
Safety and tolerability

Diclofenac

The recommended maximum daily dose of diclofenac is 150mg.

Elderly: Although the pharmacokinetics of diclofenac are not impaired to any clinically relevant extent in elderly patients, nonsteroidal anti-inflammatory drugs should be used with particular caution in such patients who generally are more prone to adverse reactions. In particular it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight and the patient should be monitored for GI bleeding during NSAID therapy.

Paracetamol

Children less than 6 years not recommended.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients.
• Active, gastric or intestinal ulcer, bleeding or perforation.
• History of gastrointestinal bleeding or perforation, relating to previous NSAID therapy.
• Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
• Last trimester of pregnancy.
• Severe hepatic, renal or cardiac failure.
• Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contraindicated in patients in whom attacks of asthma, angioedema, urticaria or acute rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs.

4.4 Special Warnings and Special Precautions for Use

General

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.
The concomitant use of diclofenac with systemic NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects.

Caution is indicated in the elderly on basic medical grounds. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.

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

Like other NSAIDs, diclofenac may mask the signs and symptoms of the infection due to its pharmacodynamic properties.

Gastrointestinal effects:

Gastrointestinal bleeding (haematemesis, melaena) ulceration or perforation which can be fatal has been reported with all NSAIDs including diclofenac and may occur at any time during treatment, with or without warning symptoms or a previous history of serious GI events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving diclofenac, the drug should be withdrawn.

As with all NSAIDs, including diclofenac close medical surveillance is imperative and particular caution should be excised when prescribing diclofenac in patients with symptoms indicative of gastrointestinal disorders, or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses including diclofenac, and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation.

The elderly have increased frequency of adverse reactions to NSAIDs especially 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 medicinal products likely to increase gastrointestinal risk.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding).

Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors (SSRIs) or anti-platelet agents such as acetylsalicylic acid.

Close medical surveillance and caution should be exercised in patients with ulcerative colitis, or with Crohn's disease as these conditions may be exacerbated.

Hepatic effects:

Close medical surveillance is required when prescribing ENZOFLAM 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), ENZOFLAM should be discontinued.
Hepatitis may occur with diclofenac without prodromal symptoms.

Caution is called for when using diclofenac in patients with hepatic porphyria, since it may trigger an attack

Renal effects:

As fluid retention and oedema have been reported in association with NSAIDs therapy, including diclofenac, particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery. Monitoring of renal function is recommended as a precautionary measure when using diclofenac in such cases. Discontinuation therapy is usually followed by recovery to the pre-treatment state

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs, including diclofenac. Patients appear to be at the highest risk of these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Diclofenac should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

LE and mixed connective tissue disease:

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis.

Cardiovascular and cerebrovascular effects:

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy including diclofenac.

Clinical trial and epidemiological data suggest that use of diclofenac, particularly at high dose (150mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with diclofenac after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking).

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

ENZOFLAM may reversibly inhibit platelet aggregation. Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.
Pre-existing asthma:

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so called intolerance to analgesics / analgesics asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria. Like other drugs that inhibit prostaglandin synthetase activity, diclofenac sodium and other NSAIDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of bronchial asthma.

Female fertility:

Diclofenac
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 severe renal or severe hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

Do not take with any other paracetamol-containing products.

If symptoms persist for more than 3 days or get worse consult your doctor.
Immediate medical advice should be sought in the event of an overdose, even if you feel well

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Diclofenac

The following interactions include those observed with diclofenac tablets.

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

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

Diuretics and antihypertensive agents: Like other NSAIDs, concomitant use of diclofenac with diuretics and antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, which should therefore be monitored frequently.

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding. Although clinical investigations do not appear to indicate that diclofenac has an influence on the effect of anticoagulants, there are isolated reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulant concomitantly. Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other nonsteroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

Other NSAIDs including cyclooxygenase-2 selective inhibitors and corticosteroids: Co-administration of diclofenac with other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration. Avoid concomitant use of two or more NSAIDs.

Antidiabetics: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However there have been isolated reports of hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Methotrexate: Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increase. Cases of serious toxicity have been reported when methotrexate and NSAIDs including diclofenac are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.

Ciclosporin: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. This might be mediated through renal antiprostagladin effects of both NSAID and calcineurin inhibitor.

Quinolone antibacterials: Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.

Phenytoin: When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

Colestipol and cholestyramine: These agents can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/ cholestyramine.

Cardiac glycosides: Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels. Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Potent CYP2C9 inhibitors: Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as sulfinpyrazone and voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

Paracetamol

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

Metoclopramide and Domperidone: The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided. Warfarin: 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.

Chloramphenicol: Increased plasma concentration of chloramphenicol.

Serratiopeptidase: Patients on anticoagulant therapy should be observed carefully because of possible potentiation of anticoagulant effects by serratiopeptidase.

4.6 Fertility, Pregnancy and Lactation

Female fertility:
As with other NSAIDs, the use of diclofenac may impair female fertility and is not recommended in women attempting to conceive. In women who may have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of diclofenac should be considered.
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 the 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.
Serratiopeptidase Not enough is known about the use of serratiopeptidase during pregnancy & lactation.

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and or cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1% up to approximately 1.5%. The risk in believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during organogenetic period. If diclofenac is used by a woman attempting to conceive, or during the 1st 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 the pregnancy, to:- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses-inhibition of uterine contractions resulting in delayed or prolonged labour
Consequently, diclofenac is contraindicated during the third trimester of pregnancy.

Lactation

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

4.7 Effects on Ability to Drive and Use Machines
None known.

4.8 Undesirable Effects
GI Effects

The most commonly-observed adverse events are GI in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis,

exacerbation of colitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed. Pancreatitis has been reported very rarely.

Hypersensitivity

Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angio-oedema and, more rarely, exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Cardiovascular

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long-term treatment) may be associated with an increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke). Vasculitis has been reported rarely.

Other Adverse Reactions Reported Less Commonly

Renal: Nephrotoxicity in various forms, including interstitial nephritis, nephritic syndrome and renal failure.

Hepatic: Abnormal liver function, hepatitis and jaundice.

Neurological and Special Senses: Visual disturbances, optic neuritis, headaches, paraesthesia, reports of aseptic meningitis (especially in patients with existing autoimmune disorders, such as SLE and mixed connective tissue disorders), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation, depression, confusion, hallucinations, tinnitus, vertigo, dizziness, malaise, fatigue and drowsiness.

Haematological: Thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia.

Dermatological: Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis (very rare). Photosensitivity.

Within the system organ classes, undesirable effects are listed under headings of frequency, using the following categories: very common (1/10); common (1/100 to <1/10); uncommon (1/1,000 to <1/100); rare (1/10,000 to <1/1,000); very rare (<1/10,000), and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. Adverse Reactions Reported in Clinical Trials

System organ class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare/ isolated reports (<1/10,000)	Not known: cannot be estimated from available data
Blood and lymphatic system disorders			Anaemia	Granulocytopenia Thrombocytopenia Neutropenia Haemolytic anaemia	
Immune system disorders			Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).	Angioneurotic oedema (including face oedema).	
Metabolism and nutrition disorders				Hyperkalemia Hypoglycaemia	
Psychiatric disorders				Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.	

System organ class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare/ isolated reports (<1/10,000)	Not known: cannot be estimated from available data
Nervous system disorders	Headache, Dizziness, drowsiness		Somnolence, tiredness	Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.	Confusion, hallucinations, disturbances of sensation, malaise
Eye disorders				Visual disturbance, vision blurred, diplopia	Optic neuritis.
Ear and labyrinth disorders	Vertigo.			Tinnitus, hearing impaired	
Cardiac disorders				Palpitations, chest pain, cardiac failure, myocardial infarction	
Vascular disorders				Flushing Hot flush, Hypertension, hypotension, vasculitis	
Respiratory, thoracic and mediastinal disorders			Asthma (including dyspnoea)	Bronchospasm Stridor, Pneumonitis.	

System organ class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare/ isolated reports (<1/10,000)	Not known: cannot be estimated from available data
Gastrointestinal disorders	Dyspepsia Abdominal pain Nausea Diarrhoea Redness of the rectal mucous membranes		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.	
Hepatobiliary disorders	Transaminases increased.		Hepatitis, jaundice, liver disorder.	Fulminant hepatitis, hepatic necrosis, hepatic failure.	

System organ class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare/ isolated reports (<1/10,000)	Not known: cannot be estimated from available data
Skin and subcutaneous tissue disorders	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				Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.	

System organ class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare/ isolated reports (<1/10,000)	Not known: cannot be estimated from available data
General disorders and administration site conditions			Oedema		
Reproductive system and breast disorders				Impotence.	

Clinical trial and epidemiological data suggest that use of diclofenac, particularly at high doses (150mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

Paracetamol
Adverse effects of paracetamol are rare and usually mild, although haematological reactions including thrombocytopenia, leucopenia, pancytopenia, neutropenia, and agranulocytosis have been reported. Skin rashes and other hypersensitivity reactions occur occasionally. Hypotension has been reported rarely with parenteral use.

Serratiopeptidase
Serratiopeptidase has few adverse effects on oral administration. Its use may cause occasional hypersensitivity, diarrhoea, nausea, vomiting, epistaxis and haemoptysis.

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 bleeding, 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 measures

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 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.

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.

If required the patient should be given intravenous-N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital.

Management of patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be discussed with the NPIS or a liver unit

Serratiopeptidase

No data available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Diclofenac sodium
Nonsteroidal anti-inflammatory drugs (NSAIDs).
Diclofenac sodium is a nonsteroidal 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 a non-opiate para-aminophenol derivative that exhibits analgesic and antipyretic activity. It does not possess anti-inflammatory activity

Serratiopeptidase
Serratiopeptidase binds to 2-macroglobulin in the blood in a 1:1 ratio. This helps to mask its antigenicity but retains its enzymatic activity. Levels of serratiopeptidase are slowly transferred to the exudates at the site of infection and inflammation and gradually blood levels decline. The mechanism of action of Serratiopeptidase appears to be hydrolysis of histamine, bradykinin and serotonin, and a proteolytic and fibrinolytic effect. Primarily this is achieved by dissolving the complement (specific proteins responsible for inflammation) and increasing the plasmin activity by inhibiting the plasmin inactivators. By the aforementioned mechanisms, Serratiopeptidase reduces capillary permeability induced by histamine, bradykinin and serotonin; breaks down abnormal exudates and proteins; facilitates the absorption of decomposed products through blood and lymphatics. Thus, Serratiopeptidase promotes wound healing and repair, and restore the skin temperature of the inflamed area, burn or trauma to normal.

Clinical Studies
Diclofenac
Applicable to 25mg Tablets only
There is limited clinical trial experience of the use of diclofenac in JRA/JIA paediatric patients. In a ramdomised, double-blind, 2 week, parallel group study in children 3-15 years with JRA/JIA, the efficacy and safety of daily 2-3 mg/kg BW diclofenac was compared with acetysalicylic acide (ASS, 50-100 mg/kg BW/d) and placebo – 15 patients in each group. In the global evaluation, 11

of 15 diclofenac patients, 6-12 asprin and 4 of 15 placebo patients showed improvement with the difference being statistically significant ($p<0.05$). The number of tender joints decreased with diclofeanc and ASS but increased with placebo. In a second randomised, double-blind, 6 week parallel group study in children aged 4-15 years with RJA/JIA, the efficacy of diclofenac (daily dose 2-3 mg/kg BW, n=22) was comparable with that of indomethacin (daily dose 2-3 mg/kg BW, n =23).

Paracetamol

5.2 Pharmacokinetic Properties

Paracetamol

Absorption and Fate

Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. It is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations. A minor hydroxylated metabolite which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause liver damage.

Serratiopeptidase

Serratiopeptidase has been shown to be absorbed from the digestive tract. On oral administration, it is absorbed unchanged into the systemic circulation, from where it penetrates into all the tissues. It reaches higher concentrations in the inflamed tissues. It attains peak levels in one hour

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf-life

24 months

6.2 Special Precautions for Storage

Protect from children.

7. Marketed By:

ALKEM LABORATORIES LTD.
ALKEM HOUSE,
Senapati Bapat Marg,
Lower Parel,
Mumbai – 400 013.