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

TRI-ZULU

1. Generic Name

Thiocolchicoside, Aceclofenac & Paracetamol Tablets

2. Qualitative and quantitative composition

Each film coated tablet contains:

Thiocolchicoside I.P……..4mg

Aceclofenac I.P…….100mg

Paracetamol I.P…….325mg

Excipients……..q.s.

Colour: Indigo Carmine

The excipients used are microcrystalline cellulose, Pregelatinized Starch, Maize Starch, PVPK 30, Talcum, Croscarmellose Sodium, Colloidal Silicon Dioxide, and Magnesium Stearate, Colorezy 17F580012 and Indigo Carmine Lake Colour.

3. Dosage Form & Strength

Dosage Form - Film Coated Tablet

Strength - Thiocolchicoside 4 mg, Aceclofenac 100 mg and Paracetamol 325 mg.

4. Clinical particulars

4.1 Therapeutic indication

For the treatment of acute inflammation conditions associated with spasm in adults only

4.2 Posology and method of administration

Dosage: As directed by the physician

4.3 Contraindications

Thiocolchicoside & Aceclofenac Tablets

Hypersensitivity to Aceclofenac or Thiocolchicoside and paracetamol or to any of the excipients.

Thiocolchicoside must not be used

- In patients hypersensitive to the active substance or to any of the excipients
- During the entire pregnancy period
- During lactation
- In women of childbearing potential not using contraception

Aceclofenac must not be used

- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- History of active bleedings or bleeding disorders.
- NSAIDS are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. Asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.
- Patients with established congestive heart failure (NYHA class II-IV), ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Severe heart failure, hepatic failure and renal failure.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDS therapy.
- Aceclofenac should not be prescribed during pregnancy, especially during the last trimester of pregnancy, unless there are compelling reasons for doing so. The lowest effective dosage should be used.
- Acute porphyria

4.4 Special warnings and precautions for use

Thiocolchicoside:

Thiocolchicoside should not be used in patients with severe renal failure Preclinical studies showed that one of Thiocolchicoside metabolites (SL59.0955) induced aneuploidy (i.e. unequal number of chromosomes in dividing cells) at concentrations close to human exposure observed at doses 8 mg twice daily. Aneuploidy is considered as a risk factor for teratogenicity, embryo/ foeto-toxicity, spontaneous abortion, and impaired male fertility and a potential risk factor for cancer. As a precautionary measure, use of the product at doses exceeding the recommended dose or long-term use should be avoided. Patients should be carefully informed about the potential risk of a possible pregnancy and about effective contraception measures to be followed.

Aceclofenac:

Elderly:

The elderly has an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

Respiratory disorders:

Caution is required if administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

Cardiovascular, Renal and Hepatic Impairment:

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with

impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients.

Renal:

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, liver dysfunction, those being treated with diuretics or recovering from major surgery. Effects on renal function are usually reversible on withdrawal of Aceclofenac Tablets.

Patients with mild to moderate renal impairment should be kept under surveillance, since the use of NSAIDs may result in deterioration of renal function. The lowest effective dose should be used and renal function monitored regularly. Effects on renal function are usually reversible on withdrawal of Aceclofenac.

Hepatic:

If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), Aceclofenac Tablets should be discontinued. Close medical surveillance is necessary in patients suffering from mild to moderate impairment of hepatic function. Hepatitis may occur without prodromal symptoms. Use of NSAIDs in patients with hepatic porphyria may trigger an attack.

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. As the cardiovascular risks of aceclofenac 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.

Aceclofenac should also be administered with caution and under close medical surveillance to patients with congestive heart failure, significant risk factors for cardiovascular events and history of cerebrovascular bleeding.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for aceclofenac.

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

Gastrointestinal bleeding, ulceration and perforation:

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

Close medical surveillance is imperative in patients with:

- symptoms indicative of gastro-intestinal disorders involving either the upper or lower gastrointestinal tract
- with a history suggestive of gastro-intestinal ulceration, bleeding or perforation
- with ulcerative colitis or with Crohn's disease
- Bleeding diathesis or Haematological abnormalities.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with hemorrhage or perforation, and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk.

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

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors or antiplatelet agents such as aspirin.

When GI bleeding or ulceration occurs in patients receiving aceclofenac, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated.

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.

Dermatological:

Impaired female fertility: The use of Aceclofenac Tablets 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 Aceclofenac Tablets should be considered.

Hypersensitivity/Dermatological reactions:

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug. Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Jonson syndrome, and toxic epidermal necrolysis, have been reporting very rarely in association with the use of NSAIDs. Patients appear to be at 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. Aceclofenac should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Exceptionally, varicella can trigger serious cutaneous and soft tissues infections complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of Aceclofenac in case of varicella.

Haematological:

Aceclofenac Tablets may reversibly inhibit platelet aggregation.

Long-term treatment:

All patients who are receiving NSAIDs should be monitored as a precautionary measure e.g. renal failure, hepatic function (elevation of liver enzymes may occur) and blood counts.

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.

Sodium methyl-, sodium ethyl- and sodium propyl- parahydroxybenzoates (E219, E215, E217) may cause allergic reactions (possibly delayed).

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

Thiocolchicoside & Aceclofenac Tablets

Other analgesics including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects.

Anti-hypertensives:

NSAIDs may reduce the effect of anti-hypertensives. The risk of acute renal insufficient, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients or elderly patients) when ACE- inhibitors or angiotensin II receptor antagonists are combined with NSAIDs. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Diuretics:

Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs. Although it was not shown to affect blood pressure control when co-administered with bendrofluazide, interactions with other diuretics cannot be ruled out. When concomitant administration with potassium-sparing diuretics is employed, serum potassium should be monitored.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR (glomerular filtration rate) and increase plasma glycoside levels.

Lithium and digoxin: Several NSAID drugs inhibit the renal clearance of lithium, resulting in increased serum concentrations of both. The combination should be avoided unless frequent monitoring of lithium and digoxin levels can be performed.

Methotrexate: Decreased elimination of methotrexate. The possible interaction between NSAIDs and methotrexate should be born in mind also when low doses of methotrexate are used, especially in patients with decreased renal function. When combination therapy has to be used, the renal function should be monitored. Caution should be exercised if NSAIDs and methotrexate are administered within 24 hours of each other, since NSAIDs may increase plasma levels, resulting in increased toxicity.

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

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding.

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin. Close monitoring of patients on combined anti-coagulants and Aceclofenac Tablets therapy should be undertaken.

Quinolone antibiotics: 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.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding.

Cyclosporine, Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus due to decreased synthesis of prostacyclin in the kidney. During combination therapy it is therefore important to carefully monitor renal function.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and hematoma in HIV (+) hemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Antidiabetic agents: 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. Thus with Aceclofenac Tablets, consideration should be given to adjustment of the dosage of hypoglycaemic agents.

Other NSAIDs: Concomitant therapy with aspirin or other NSAIDs may increase the frequency of adverse reactions, including the risk of GI bleeding.

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.)

Thiocolchicoside

Pregnancy

There are limited data on the use of thiocolchicoside in pregnant women. Therefore, the potential hazards for the embryo and foetus are unknown. Studies in animals have shown teratogenic effects. is contraindicated during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding

Since it passes into the mother's milk, the use of thiocolchicoside is contraindicated during breastfeeding.

Fertility

In a fertility study performed in rats, no impairment of fertility was seen at doses up to 12 mg/kg, i.e. at dose levels inducing no clinical effect. Thiocolchicoside and its metabolites exert aneugenic activity at different concentration levels, which is a risk factor for impairment of human fertility.

Aceclofenac

Pregnancy

There is no information on the use of Aceclofenac during 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, cardiac malformation or gastroschisis after use of 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. During the first and second trimester of pregnancy, Aceclofenac should not be given unless clearly necessary. If Aceclofenac is used by a women attempting to conceive, or during the first the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern.

In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of the ductus arteriosus) and on the possible risk of persistent pulmonary hypertension of the new born, use in the last trimester of pregnancy is contraindicated. NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

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 with an increased bleeding tendency in both mother and child.

Consequently, Aceclofenac is contraindicated during the third trimester of pregnancy

Lactation:

There is no information on the secretion of Aceclofenac to breast milk, there was however no notable transfer of radio labelled (14C) Aceclofenac to the milk of lactating rats.

The use of Aceclofenac Tablets should therefore be avoided in pregnancy and lactation unless the potential benefits to the other outweigh the possible risks to the foetus.

Fertility:

NSAIDs may impair fertility and are not recommended in women trying to conceive. The temporary discontinuation of Aceclofenac should be considered in women having difficulties to conceive or undergoing investigations for infertility.

Paracetamol

Pregnancy

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.

Lactation:

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

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

4.8 Undesirable effects

Thiocolchicoside & Aceclofenac Tablets

The following undesirable effects include those reported with both the drugs

Blood and lymphatic system disorders

Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis

Immune system disorders

Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock), Angioneurotic oedema (including face oedema)

Psychiatric disorders

Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder/reactions, confusion, hallucinations

Nervous system disorders

Headache, dizziness, Somnolence, drowsiness, tiredness, hypotension, Paraesthesia, memory impairment/disturbance, convulsion, anxiety, tremor, taste disturbances, cerebrovascular accident, disturbances of sensation, taste disturbances, malaise, aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus and mixed tissue disease) with symptoms such as fever, stiff neck, headache, nausea and vomiting.

Eye disorders

Visual disturbance, vision blurred, diplopia, optic neuritis

Ear and labyrinth disorders

Vertigo, Tinnitus, hearing impaired

Cardiac disorders

Palpitations, chest pain, cardiac failure/congestive heart failure, myocardial infarction

Vascular disorders

Hypertension, vasculitis

Respiratory, thoracic and mediastinal disorders

Asthma (including dyspnoea), alveolitis, pulmonary eosinophilia, Pneumonitis, Aggravated asthma or bronchospasm have also been reported

Gastrointestinal disorders

Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain or cramps, flatulence, anorexia, Gastritis, gastrointestinal haemorrhage or bleeding, haematemesis, diarrhoea hemorrhagic/bloody, melaena, gastrointestinal ulcer, with or without bleeding or perforation, colitis (including colonic damage, nonspecific hemorrhagic colitis/ hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease/Crohn's proctocolitis), constipation, stomatitis/ aphthous stomatitis, glossitis, oesophageal disorder/lesions, diaphragm-like intestinal strictures/stricture formation, pancreatitis

Hepatobiliary disorders

Transaminases (serum aminotransferase enzymes) increased (eg AST, ALT), Hepatitis, jaundice, liver disorder, Fulminant hepatitis

Skin and subcutaneous tissue disorders

Rash, skin eruptions, Urticaria, Bullous eruptions/dermatoses, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis/acute toxic epidermolysis (Lyell's syndrome), dermatitis exfoliative (erythroderma), loss of hair, photosensitivity reactions, purpura, allergic purpura, pruritus

Renal and urinary disorders

Interstitial fibrosis has been reported with NSAIDs and may lead to renal failure, acute renal failure or insufficiency, urinary abnormalities (eg hematuria, proteinuria), nephrotic syndrome, interstitial nephritis, renal papillary necrosis

General disorders and administration site conditions

Oedema, Impotence

Post marketing experience:

Stevens Johnson syndrome (SJS) and Toxic Epidermal

Paracetamol

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

Post marketing data

Body System	Undesirable effect
Blood and lymphatic system disorders	Thrombocytopenia Agranulocytosis
Immune system disorders	Anaphylaxis Cutaneous hypersensitivity reactions including skin rashes, angiodema and Stevens Johnson syndrome/toxic epidermal necrolysis
Respiratory, thoracic and mediastinal disorders	Bronchospasm*
Hepatobiliary disorders	Hepatic dysfunction

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

4.9 Overdose

Thiochichoside

At higher doses, thiocolchicoside induced diarrhea and convulsions in both rodents and non-rodents after acute administration by oral route. After repeated administration, thiocolchicoside

induced gastro-intestinal disorders (enteritis, emesis) by oral route, and emesis by i.m. route. No overdosage symptoms have been reported in patients treated with thiocolchicoside. Should over dosage occurs, medical supervision and symptomatic measures are recommended.

Aceclofenac

There is insufficient data available on the consequences of Aceclofenac in humans.

a) Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal irritation, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, hypotension, respiratory depression, fainting, occasionally and convulsions. In cases of significant poisoning acute renal failure and liver damage are possible.

b) Therapeutic measure: Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose. Given the route of administration and the pharmaceutical form, an overdose with injectable Aceclofenac is unlikely.

Specific therapies such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism. Good urine output should be ensured.

Renal and liver function should be closely monitored. Patients should be observed for at least four hours after ingestion of potentially toxic amounts. In case of frequent or prolonged convulsions, patients should be treated with intravenous diazepam. Other measures may be indicated by the patient's clinical condition.

Management of acute poisoning with NSAIDs essentially consists of supportive and symptomatic measures.

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

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

b) regularly consumes ethanol in excess of recommended amounts.

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

Thiocolchicoside

Thiocolchicoside exhibits a selective affinity for the inhibitory gamma-aminobutyric acid and glycinergic receptors

Aceclofenac

The mode of action of aceclofenac is largely based on the inhibition to prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclo-oxygenase, which is involved in the production of prostaglandins.

Paracetamol

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

5.2 Pharmacodynamicproperties

Thiocolchicoside

ATC code: MO3BX03

It has an agonistic action at the spinal-strychnine-sensitive receptors that could mediate its myorelaxant effect. However, experimental and clinical evidence strongly suggest a proconvulsant action for thiocolchicoside. Interaction with glycine receptors does not explain the convulsant action of the molecule. It has been suggested that thiocolchicoside might preferentially interact with a cortical subtype of the gamma aminobutyric acid type A (GABAA) receptor that expresses low-affinity binding sites for GABA. The low-affinity recognition site seems to be an antagonist-binding site. This explains the proconvulsant effect of thiocolchicoside. This is in contrast to earlier studies that suggested a GABA mimetic effect which would explain its muscle relaxant property. GABAB receptors are largely unaffected by

thiocolchicoside and hence do not contribute to its muscle relaxation action. Hence, the exact mechanism for muscle relaxation is yet to be known, although from available evidence, inhibition of glycine receptors is a possible mechanism.

Aceclofenac

Aceclofenac is a non-steroidal agent with marked anti-inflammatory and analgesic properties.

ATC code: M01A B16

The mode of action of aceclofenac is largely based on the inhibition to prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclo-oxygenase, which is involved in the production of prostaglandins.

Paracetamol

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

Clinical Efficacy

In 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

Thiocolchicoside

Absorption: After IM administration, thiocolchicoside Cmax occur in 30 min and. reach values of 113 ng/mL after a 4 mg dose and 175 ng/mL after a 8 mg dose. The corresponding values of AUC are respectively 283 and 417 ng.h/mL. The pharmacologically active metabolite SL18.0740 is also observed at lower concentrations with a Cmax of 11.7 ng/mL occurring 5 h post dose and an AUC of 83 ng.h/mL. No data are available for the inactive metabolite SL59.0955. - After oral administration, no thiocolchicoside is detected in plasma. Only two metabolites are observed: The pharmacologically active metabolite SL18.0740 and an inactive metabolite SL59.0955. For both metabolites, maximum plasma concentrations occur 1hour after thiocolchicoside administration. After a single oral dose of 8 mg of thiocolchicoside the Cmax and AUC of SL18.0740 are about 60 ng/mL and 130 ng.h/mL respectively. For SL59.0955 these values are much lower: Cmax around 13 ng/mL and AUC ranging from 15.5 ng.h/mL (until 3h) to 39.7 ng.h/mL (until 24h).

Distribution: The apparent volume of distribution of thiocolchicoside is estimated around 42.7 L after an IM administration of 8 mg. No data are available for both metabolites.

Biotransformation: After oral administration, thiocolchicoside is first metabolized in the aglycon 3- demethyltiocolchicine or SL59.0955. This step mainly occurs by intestinal metabolism explaining the lack of circulating unchanged thiocolchicoside by this route of administration. SL59.0955 is then glucuroconjugated into SL18.0740 which has equipotent

pharmacological activity to thiocolchicoside and thus supports the pharmacological activity after oral administration of thiocolchicoside. SL59.0955 is also demethylated into didemethyl-thiocolchicine.

Elimination:

After IM administration the apparent t1/2 of thiocolchicoside is 1.5h and the plasma clearance 19.2 L/h. - After oral administration, total radioactivity is mainly excreted in feces (79%) while urinary excretion represents only 20%. No unchanged thiocolchicoside is excreted either in urine or feces. SL18.0740 and SL59.0955 are found in urine and feces while the didemethyl-thiocolchicine is only recovered in feces. After oral administration of thiocolchicoside, the SL18.0740 metabolites is eliminated with an apparent t1/2 ranging from 3.2 to 7 hours and the metabolite SL59.0955 has a t1/2 averaging 0.8h.

Aceclofenac

After oral administration, aceclofenac is rapidly and completely absorbed as unchanged drug. Peak plasma concentrations are reached approximately 1.25 to 3.00 hours following ingestion. Aceclofenac penetrates into the synovial fluid, where the concentrations reach approximately 57% of those in plasma. The volume of distribution is approximately 25 L.

The mean plasma elimination half-life is around 4 hours. Aceclofenac is highly protein- bound (>99%). Aceclofenac circulates mainly as unchanged drug. 4'- hydroxy aceclofenac is the main metabolite detected in plasma. Approximately two- thirds of the administered dose is excreted via the urine, mainly as hydroxymetabolites.

No changes in the pharmacokinetics of aceclofenac have been detected in the elderly.

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 500 mg Tablets contain a disintegrant system which accelerates tablet dissolution compared to standard paracetamol tablets.

Human scintigraphy data demonstrate that Paracetamol Advance 500 mg Tablets 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 Advance 500 mg Tablets 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 Advance 500 mg Tablets compared to standard paracetamol tablets ($P<0.05$).

Total extent of absorption of paracetamol from Paracetamol Advance 500 mg Tablets is equivalent to that from standard paracetamol tablets.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Thiochichoside

Thiocolchicoside profile has been assessed in vitro, and in vivo following parenteral and oral administration. Thiocolchicoside was well tolerated following oral administration for periods of up to 6 months in both the rat and the non-human primate when administered at repeated doses of less than or equal to 2 mg/kg/day in the rat and less or equal to 2.5 mg/kg/day in non-human primate, and by the intramuscular route in the primate at repeated doses up to 0.5 mg/kg/day for 4 weeks.

At high doses, thiocolchicoside induced emesis in dog, diarrhoea in rat and convulsions in both rodents and non-rodents after acute administration by oral route.

After repeated administration, thiocolchicoside induced gastro-intestinal disorders (enteritis, emesis) by oral route and emesis by IM route.

Thiocolchicoside itself did not induce gene mutation in bacteria (Ames test), in vitro chromosomal damage (chromosome aberration test in human lymphocytes) and in vivo chromosomal damage (in vivo micronucleus in mouse bone marrow administered intraperitoneally).

The major glucuro-conjugated metabolite SL18.0740 did not induce gene mutation in bacteria (Ames test); however, it induced in vitro chromosomal damage (in vitro micronucleus test on human lymphocytes) and in vivo chromosomal damage (in vivo micronucleus test in mouse bone marrow administered orally). The micronuclei predominantly resulted from chromosome loss (centromere positive micronuclei after FISH centromere staining), suggesting aneugenic properties. The aneugenic effect of SL18.0740 was observed at concentrations in the in vitro test and at AUC plasma exposures in the in vivo test higher (more than 10 fold based on AUC) than those observed in human plasma at therapeutic doses.

The aglycon metabolite (3-demethylthiocolchicine-SL59.0955) formed mainly after oral administration induced in vitro chromosomal damage (in vitro micronucleus test on human lymphocytes) and in vivo chromosomal damage (in vivo oral micronucleus test in rat bone marrow administred orally). The micronuclei predominantly resulted from chromosome loss (centromere positive micronuclei after FISH or CREST centromere staining), suggesting aneugenic properties. The aneugenic effect of SL59.0955 was observed at concentrations in the in vitro test and at exposures in the in vivo test close to those observed in human plasma at therapeutic doses of 8 mg twice daily per os. Aneugenic effect in dividing cells may result in aneuploidy cells. Aneuploidy is a modification in the number of chromosomes and loss of heterozygosity, which is recognized as a risk factor for teratogenicity, embryotoxicity/ spontaneous abortion, impaired male fertility, when impacting germ cells and a potential risk factor for cancer when impacting somatic cells. The presence of the aglycon metabolite (3-demethylthiocolchicine-SL59.0955) after intramuscular administration has never been assessed, therefore its formation using this route of administration cannot be excluded.

In the rat, an oral dose of 12 mg/kg/day of thiocolchicoside caused major malformations along with fetotoxicity (retarded growth, embryo death, impairment of sex distribution rate). The dose without toxic effect was 3 mg/kg/day.

In the rabbit, thiocolchicoside showed maternotoxicity starting from 24 mg/kg/day. Furthermore, minor abnormalities have been observed (supernumerary ribs, retarded ossification).

In a fertility study performed in rats, no impairment of fertility was seen at doses up to 12 mg/kg/day, i.e. at dose levels inducing no clinical effect. Thiocolchicoside and its metabolites exert aneugenic activity at different concentration levels, which is recognized as a risk factor for impairment of human fertility.

The carcinogenic potential was not evaluated

Aceclofenac

The results from preclinical studies conducted with Aceclofenac are consistent with those expected for NSAIDs. The principal target organ was the gastro-intestinal tract.

No unexpected findings were recorded.

Aceclofenac was not considered to have any mutagenic activity in three in vitro studies and an in vivo study in the mouse.

Aceclofenac was not found to be carcinogenic in either the mouse or rat.

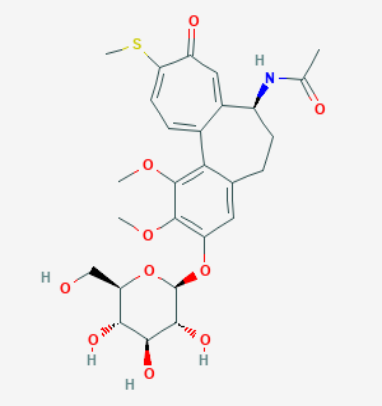
Paracetamol

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

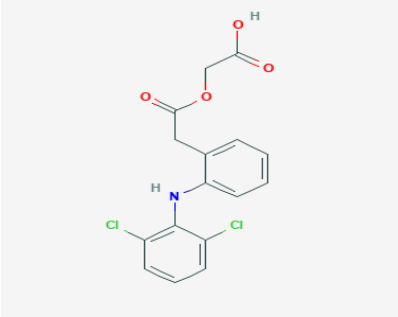
Thiocolchicoside

Thiocolchicoside is chemically N-[(7S)-1,2-dimethoxy-10-methylsulfanyl-9-oxo-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-6,7-dihydro-5H-benzo[a]heptalen-7-yl]acetamide having molecular weight of 563.6 g/mol and molecular formula is C27H33NO10S with the chemical structure as below:



Aceclofenac

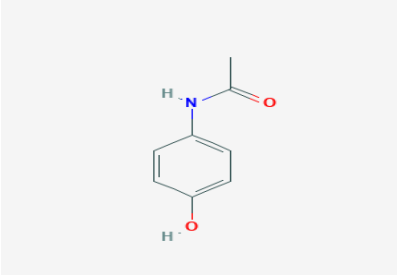
Aceclofenac is 2-[(2,6-dichlorophenyl)amino]phenylacetoxyacetic acid having empirical formula C16H13Cl2NO4 and molecular weight is 354.2. The chemical structure is:



Aceclofenac is white or almost white, crystalline powder which is freely soluble in acetone; soluble in ethanol (95%); practically insoluble in water.

Paracetamol

Paracetamol is 4-hydroxyacetanilide having molecular formula of C8H9NO2 and molecular weight is 151.2 and the chemical structure is:



Paracetamol is white crystals or white, crystalline powder which is freely soluble in ethanol (95%) and in acetone; sparingly soluble in water; very slightly soluble in dichloromethane and in ether.

Thiocolchicoside, Aceclofenac & Paracetamol Tablets are blue colour, capsule shaped, biconvex, film coated tablets having scored on one side and other side plain. The excipients used are Microcrystalline cellulose, Pregelatinized Starch, Maize Starch, PVPK 30, Talcum, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate, Colorezy 17F580012 and Indigo Carmine Lake Colour.

8. Pharmaceutical particulars

8.1 Incompatibilities

None known.

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

TRI-ZULU is available in Blister strip of 10 Tablets.

8.4 Storage and handing instructions

Store in a dry and dark place at a temperature not exceeding 30°C.

Keep the medicines out of reach of children.

9. Patient Counselling Information

9.1 What TRI-ZULU is and what it is used for

Tri-zulu is combination of Aceclofenac, Thiocolchicoside and paracetamol. This medicine is used a muscle relaxant. Tablets are combination of a non-steroidal anti-inflammatory drugs (NSAIDs). It is used for the treatment of acute inflammation conditions associated with spasm in adults only

9.2 What you need to know before you take

Do not take TRI-ZULU if:

- You are allergic to thiocolchicoside or any of the other ingredients of this medicine - you are pregnant, might become pregnant or think you may be pregnant
- You are a woman of childbearing potential not using contraception
- You are breast feeding taking other medicines containing paracetamol.

Warnings and precautions

Strictly respect the doses and duration of treatment detailed in section 3. You should not use this medicine at higher dose or for longer than 7 days (for oral forms)/5 days (for IM forms). This is because one of the products formed in your body when taking thiocolchicoside at high doses might cause damage to some cells (abnormal number of chromosomes). This has been shown in studies in animals and in laboratory studies. In humans, this type of damage to cells is a risk factor for cancer, harm to the unborn child, and impairment of male fertility. Please discuss with your doctor if you have further questions. Your doctor will inform you about all measures relating to an effective contraception and about the potential risk of a pregnancy.

Children and adolescents

Do not give this medicine to children and adolescents below 16 years old because of safety concerns.

Pregnancy, breast-feeding and fertility

Do not take this medicine if: - you are pregnant, might become pregnant or think you may be pregnant - you are a woman of childbearing potential not using contraception

This is because this medicine may harm your unborn child. Do not take this medicine if you are breast-feeding. This is because the medicine passes into your breast-milk. This medicine might cause problems to the male fertility due to potential damage to sperm cells (abnormal number of chromosomes). This is based on laboratory studies

Other medicines and TRI-ZULU

Talk to your doctor or pharmacist before taking these tablets if you are taking any prescribed medicines; particularly metoclopramide or domperidone (for nausea [feeling sick] or vomiting [being sick]) or colestyramine (to lower blood cholesterol) if you take blood thinning drugs (anticoagulants e.g. warfarin) and you need to take a pain reliever on a daily basis, talk to your doctor because of the risk of bleeding. Please take your doctor’s advice.

Medicines used to treat high blood pressure (antihypertensives: ACE inhibitors or angiotensin II receptor antagonists; when taken with **TRI-ZULU** may reduce kidney function special in elderly patients. Ask your doctor before starting

Drugs used to increase the rate of urine excretion (diuretics) can increase risk to the kidney and decrease effects of diuretics when taken concomitantly.

Cardiac glycosides**: TRI-ZULU** - may exacerbate cardiac failure, reduce GFR (glomerular filtration rate) and increase plasma glycoside levels.

Ask your doctor before starting Lithium and digoxin, Methotrexate

If you take Mifepristone ask your doctor how to take it

Medicines to treat infection (quinolone antibiotics such as ciprofloxacin, ofloxacin, levofloxacin moxifloxacin) when taken concomitantly may cause convulsion.

Medicines used to treat HIV (zidovudine) when taken with **TRI-ZULU** may Increase risk of haematological toxicity

Medicines used to lower blood sugar levels in diabetes (antidiabetics such as glibenclamide, glycoside, and tolbutamide) when taken with **TRI-ZULU dose should be adjusted by physician.**

Concomitant therapy with aspirin or other NSAIDs may increase the frequency of adverse reactions, including the risk of GI bleeding.

9.3 How to take TRI-ZULU

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Dosage: As directed by the physician.

If you take more TRI-ZULU than you should

If you accidentally take more TRI-ZULU than you should talk to your doctor, pharmacist or nurse.

If you forget to take TRI-ZULU

Do not take a double dose to make up for a forgotten dose. If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

If you stop taking TRI-ZULU

Do not stop taking **TRI-ZULU** unless your doctor advises you.

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

9.4 Possible side effects

Like all medicines, TRI-ZULU can have side effects but not everybody gets them. A small number of people have had side effects. Stop taking the medicine and tell your doctor immediately if you experience:

- Allergic reactions which may be severe such as skin rash and itching sometimes with swelling of the mouth or face or shortness of breath

- Skin rash or peeling, or mouth ulcers
- Breathing problems. These are more likely if you have experienced them before when taking other painkillers such as ibuprofen and aspirin
- Unexpected bruising or bleeding
- Nausea, sudden weight loss, loss of appetite and yellowing of the eyes and skin. If you do get any side effects, even those not mentioned in this leaflet, tell your doctor or pharmacist.

Other Adverse Events:

Blood disorders

Such as reduced production of blood cells, abnormal breakdown of red blood cells known as haemolytic anemia, low content of iron in the blood, low level of white blood cells, low number of platelet cells If any of the below side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Severe allergic reaction (anaphylactic shock). Symptoms may develop as decreased blood pressure swelling of the face and throat

Psychiatric disorders

Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder/reactions, confusion, hallucinations

Nervous system disorders

Headache, dizziness, **sleepiness**" or "**drowsiness** tiredness, decreased blood pressure, abnormal sensation, memory impairment/disturbance, convulsion, anxiety, tremor, taste disturbances, cerebrovascular accident, disturbances of sensation, taste disturbances, malaise, aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus and mixed tissue disease) with symptoms such as fever, stiff neck, headache, nausea and vomiting

Eye disorders

Visual disturbance, vision blurred, double vision.

Ear and labyrinth disorders

Spinning is in the head, ringing or buzzing noise in the ears and hearing impaired

Cardiac disorders
Irregular beating of the heart***, chest pain and heart failure.***

Vascular disorders

Decreased blood pressure and inflammation of blood vessels.

Respiratory, thoracic and mediastinal disorders

Asthma (including dyspnoea), impaired functioning of lung.

Gastrointestinal disorders

Feeling sick, vomiting, diarrhoea, dyspepsia, abdominal pain or cramps, flatulence, decreased

appetite, inflammation in stomach or bleeding, haematemesis, diarrhoea hemorrhagic/bloody, melaena, gastrointestinal ulcer, with or without bleeding or perforation, colitis (including colonic damage, nonspecific hemorrhagic colitis/ hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease/Crohn's proctocolitis), constipation, inflammation of pancreas

Hepatobiliary disorders

Inflammation of liver, disturbed function of liver and jaundice.

Skin and subcutaneous tissue disorders

Sever Rash, skin eruptions, eczema, erythema, erythema multiforme, inflammation of skin, redness and swollen of skin loss of hair, photosensitivity reactions Allergic reaction of skin.

Renal and urinary disorders

Kidney failure, insufficiency, urinary abnormalities (eg blood in urine, protein in urine), General disorders and administration site conditions

Condition characterized by an excess of watery fluid collecting in the cavities or tissues of the body., Impotence

Post marketing experience:

Stevens Johnson syndrome (SJS) and Toxic Epidermal (are severe cutaneous hypersensitivity reactions. Drug causes. Macules rapidly spread and coalesce, leading to **epidermal** blistering, necrosis, and sloughing.)

9.5 How to store TRI-ZULU

Store in a dry and dark place at a temperature not exceeding 30°C.

9.6 Contents of the pack and other information

Each film coated tablet contains:

Thiocolchicoside I.P 4mg

Aceclofenac I.P 100mg

Paracetamol I.P 325mg

The excipients used are microcrystalline cellulose, Pregelatinized Starch, Maize Starch, PVPK 30, Talcum, Croscarmellose Sodium, Colloidal Silicon Dioxide, and Magnesium Stearate, Colorezy 17F580012 and Indigo Carmine Lake Colour.

10. Details of manufacturer

Manufactured in India by:

Ravenbhel Healthcare Pvt Ltd.

(WHO & cGMP Certified Company)

16-17, EPIP, SIDCO, Kartholi, Bari Brahmana, Jammu – 181133.

11. Details of permission or licence number with date

Mfg Lic No. JK/01/56 issued on 14.05.2015

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/TRI-ZULU 4, 100, 325 mg/MAY-20/01/PI