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

TOROXX AP

(Aceclofenac And Paracetamol Tablets) (with β-Cyclodextrin)

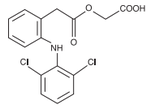
COMPOSITION:

Each uncoated tablet contains :

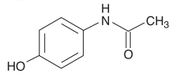
Aceclofenac I.P.	100 mg
Paracetamol I.P.	500 mg
(with β-Cyclodextrin)	
Excipients	q.s.

DESCRIPTION :

Toroxx AP is fixed dose combination of Aceclofenac 100 mg and Paracetamol 500 mg. Aceclofenac is a novel NSAID known to produce multifactor mechanism of action. Aceclofenac is a White or almost white, crystalline powder. Practically insoluble in water; freely soluble in acetone; soluble in ethanol (95%) Chemically, Aceclofenac is [(2,6-dichlorophenyl) amino]phenylacetoxyacetic acid. The empirical formula is $C_{16}H_{13}Cl_2NO_4$ and its molecular weight is 354.2.



Paracetamol is White crystals or a white, crystalline powder. It is freely soluble in ethanol (95%) and in acetone; sparingly soluble in water; very slightly soluble in dichloromethane and ether. Paracetamol a peripherally acting analgesic. Chemically, Paracetamol is 4-hydroxyacetanilide. The empirical formula is $C_8H_9NO_2$ and its molecular weight is 151.2.



PHARMACOLOGY

Pharmacodynamic

Aceclofenac

Aceclofenac is an orally effective NSAID of the phenylacetic acid group, which has anti-inflammatory and analgesic actions. 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. Aceclofenac provides symptomatic relief in a variety of clinical conditions associated with pain and inflammation. Efficacy of Aceclofenac is comparable to other NSAIDs with regard to relief of pain and control of inflammation. Aceclofenac has favorable gastro-intestinal tolerance profile. The analgesic effect of Aceclofenac on the pain induced experimentally by chemical and mechanical stimuli was nearly equal to that of Indomethacin and Diclofenac. In patients with osteoarthritis of knees, Aceclofenac decreases pain, reduces disease severity and improves functional capacity of the knee. Aceclofenac reduces joint inflammation, pain and the duration of morning stiffness in patients with rheumatoid arthritis. The duration of morning stiffness and pain are reduced and spinal mobility improved by Aceclofenac in patients with ankylosing spondylitis. Aceclofenac is also effective in painful conditions in dental and gynaecological practice.

Paracetamol

Paracetamol produces analgesic and antipyretic as main effects and it has been also reported that paracetamol has a weak anti-inflammatory effect. Analgesic action: The central analgesic action of Paracetamol resembles that of aspirin. It produces analgesia by raising pain threshold. Antipyretic effect: The antipyretic effect of Paracetamol is attributed to its ability to inhibit COX in the brain where peroxide tone is low. Recent evidence suggests inhibition of COX-3 (believed to be splice variant product of the COX-1 gene) could represent a primary central mechanism by which Paracetamol decreases pain and possibly fever.

Pharmacokinetic

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 25L. The mean plasma elimination half-life is around 4 hours. Aceclofenac is highly protein-bound > 99%. Aceclofenac circulates mainly as unchanged drug 4'-Hydroxyaceclofenac 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 gastrointestinal tract with peak plasma concentrations (C_{max}) occurring about 10 to 60 minutes after oral administration. Plasma protein binding is negligible at usual therapeutic concentration but increases with increasing concentrations. Acetaminophen is distributed throughout most body fluids. The plasma half life ($t_{1/2}$) 1-4 hours and the effect after oral dose lasts for 3-5 hours. Paracetamol is metabolized primarily in liver and excreted in the urine mainly as glucuronide and sulfate conjugate.

INDICATIONS

Toroxx AP is indicated for acute painful condition in adults only.

CONTRAINDICATION

Hypersensitivity to aceclofenac (or its analogue diclofenac) or paracetamol or to any of the excipients Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding). NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.

Severe heart failure, hepatic failure and renal failure

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Aceclofenac and paracetamol 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.

WARNINGS AND PRECAUTIONS

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms. The use of aceclofenac with concomitant NSAIDs including cyclooxygenase- 2 selective inhibitors should be avoided.

Elderly:

The elderly have 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 importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, those being treated with diuretics or recovering from major surgery. 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 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 aceclofenac 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. 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, 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, with a history suggestive of gastro-intestinal ulceration, 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 haemorrhage 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:

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. 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. Aceclofenac should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Impaired female fertility:

The use of aceclofenac 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 should be considered.

Hypersensitivity reactions:

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug.

Haematological:

Aceclofenac 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

Paracetamol should be given with care to patients with impaired kidney or liver function. It should also be given with care to patients with alcohol dependence.

PREGNANCY AND LACTATION

Aceclofenac

Pregnancy:

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. The regular use of NSAIDs during the last trimester of pregnancy may decrease uterine tone and contraction. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child. 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. Animal studies indicate that there was no evidence of teratogenesis in rats although the systemic exposure was low and in rabbits, treatment with aceclofenac (10 mg/kg/day) resulted in a series of morphological changes in some foetuses.

Lactation:

In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding. The use of aceclofenac should therefore be avoided in pregnancy and lactation unless the potential benefits to the other outweigh the possible risks to the foetus.

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.

Interaction with other medicinal products:

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: Reduced anti-hypertensive effect.

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: Decreased elimination of lithium

Methotrexate: Decreased elimination of methotrexate. 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.

Ciclosporin: Increased risk of nephrotoxicity.

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 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.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

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

Antidiabetic agents: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents with influencing their clinical effect. However, there have been isolated reports of hypoglycaemic and hyperglycaemic effects. Thus with aceclofenac, 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.The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes. The absorption of paracetamol may be accelerated by drugs such as metoclopramide. Excretion may be affected and plasma concentrations altered when given with probenecid. Colestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.

ADVERSE EFFECTS

Gastrointestinal: The most commonly-observed adverse events are gastrointestinal 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, angiodema and, more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Cardiovascular and cerebrovascular: 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 (for example myocardial infarction or stroke).

The majority of adverse reactions reported have been reversible and of a minor nature. The most frequent are gastro-intestinal disorders, in particular dyspepsia, abdominal pain, nausea and diarrhoea, and occasional occurrence of dizziness. Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment. *Dermatological complaints including pruritus and rash and Investigations:* Abnormal hepatic enzyme and serum creatinine levels have also been reported.

Other adverse reactions reported less commonly include:

Renal: Nephrotoxicity in various forms, including interstitial nephritis, nephrotic 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 auto immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), 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.

If serious adverse reactions occur, aceclofenac should be withdrawn.

The following is a table of adverse reactions reported during clinical studies and after authorization, grouped by System-Organ Class and estimated frequencies.

MedDRA SOC isolated	Common < 10%- >1%	Uncommon < 1% - > 0.1%	Rare < G.1%- > 0.01%	Very rare/ reports < 0.01%
Blood and lymphatic system disorders			Anaemia	Granulocytopenia Thrombocytopenia Neutropenia Haemolytic anaemia
Immune system disorders			Anaphylactic reaction (including shock) Hypersensitivity	
Metabolism and nutrition disorders				Hyperkalemia
Psychiatric disorders				Depression Abnormal dreams Insomnia
Nervous system disorders	Dizziness			Paraesthesia Tremor Somnolence Headache Dysgeusia (abnormal taste)
Eye disorders			Visual disturbance	
Ear and labyrinth disorders				Vertigo
Cardiac disorders				Palpitations
Vascular disorders				Flushing, Hot flush
Respiratory, thoracic and mediastinal disorders			Dyspnoea	Bronchospasm Stridor
Gastrointestinal disorders	Dyspepsia Abdominal pain Nausea Diarrhoea	Flatulence Gastritis Constipation Vomiting Mouth ulceration	Melaena	Stomatitis Haematemesis Gastrointestinal haemorrhage Gastric ulcer Pancreatitis
Hepatobiliary disorders				Hepatitis Jaundice
Skin and subcutaneous tissue disorders		Pruritus Rash Dermatitis Urticaria	Face oedema	Purpura Dermatitis bullous
Renal and urinary disorders				Renal insufficiency Nephrotic syndrome
General disorders and administration site conditions				Oedema Fatigue Cramps in legs
Investigations	Hepatic enzyme increased	Blood urea increased Blood creatinine increased		Blood alkanine phosphatase increased Weight increase

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.

OVERDOSAGE

Aceclofenac:

a) Symptoms

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal irritation, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, hypotension, respiratory depression, fainting, occasionally 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.

Specific therapies such as dialysis or haemoperfusion are probable 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.

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.

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.

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.

Caution : Overdose of Paracetamol may be injurious to liver.

DOSAGE

Toroxx AP is recommended twice a day, by mouth.

EXPIRY DATE

Do not use after the date of expiry.

STORAGE

Store in a dry place at a temperature not exceeding 25°C.

Keep all the medicines out of reach of children.

PRESENTATION:

Toroxx AP is available in blister pack of 10 tablets.

torrent

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
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