APPROVED PROFESSIONAL INFORMATION

PROFESSIONAL INFORMATION:

SCHEDULING STATUS:

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1. NAME OF THE MEDICINE:

ACUTEV (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each film-coated tablet contains 500 mg paracetamol.

ACUTEV is sugar free.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Film-coated tablets.

White to off-white, oval shaped biconvex tablet, break-line on one side of the tablet and plain on the other side.

Dimensions: approx. 7,9 × 17,1 mm. The height of the tablet is approx. 5,0 to 6,5 mm.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

ACUTEV is indicated for the symptomatic relief of mild to moderate pain and fever such as headache, migraine, backache, muscle pains, sore throat, toothache, pain and fever associated with colds and flu.

4.2 Posology and method of administration:

Posology:

DO NOT EXCEED THE RECOMMENDED DOSE.

The lowest dose necessary to achieve efficacy should be used for the shortest duration of treatment.

Should not be used with other paracetamol-containing medicines.

Not more than four doses in any 24-hour period. Maximum daily dose: 4 000 mg.

Minimum dosing interval: 4 hours.

Adults (including the elderly) and children aged 16 years and over:

One to two film-coated tablets every 4 to 6 hours as required.

Maximum daily dose: 4 000 mg (8 film-coated tablets).

Children, 10 to ≤ 15 years of age:

One film-coated tablet every four to six hours as required.

No more than four doses in any 24-hour period.

Maximum duration of continued use without medical advice: 3 days.

Maximum daily dose: 60 mg/kg presented in four divided doses of 10-15 mg/kg throughout the 24-hour period.

Paediatric population:

Children under 10 years:

Not recommended for children under 10 years of age.

Method of administration:

Oral administration only.

4.3 Contraindications:

- Hypersensitivity to paracetamol or to any of the excipients of ACUTEV listed in **section 6.1**.
- Severe hepatic impairment (Child Pugh C).

4.4 Special warnings and precautions for use:

ACUTEV contains paracetamol which may be fatal in overdose.

In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or Poison Centre must be contacted immediately.

DO NOT EXCEED THE RECOMMENDED DAILY DOSE.

Dosages in excess of those recommended may cause severe liver damage.

ACUTEV contains paracetamol. Do not use with any other paracetamol-containing medicines. The concomitant use with other medicines containing paracetamol may lead to an overdose.
Paracetamol overdose may cause liver failure which may require liver transplant or lead to death.

Underlying liver disease increases the risk of paracetamol-related liver damage. Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking ACUTEV.

Cases of hepatic dysfunction/failure have been reported in patients with depleted glutathione levels, such as those who are severely malnourished, anorexic, have a low body mass index, are chronic heavy users of alcohol or have sepsis.

In patients with glutathione depleted states the use of paracetamol may increase the risk of metabolic acidosis.

If symptoms persist, medical advice must be sought.

Patients should not use ACUTEV tablets continuously for longer than 10 days without consulting their medical practitioner.

Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking ACUTEV tablets.

Severe cutaneous adverse reactions (SCARs):

Severe cutaneous adverse reactions (SCARs) such as Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), Acute generalised exanthematous pustulosis (AGEP), Drug reaction with eosinophilia and systemic symptoms (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and Fixed drug eruptions (FDE) have been reported in patients treated with paracetamol containing medicines. If a patient develops SCARs, with symptoms that include skin reddening, blisters and rash, treatment with ACUTEV tablets must immediately be discontinued and appropriate treatment instituted (see **section 4.8**).

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism), who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of

paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring, is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as an underlying cause of HAGMA in patients with multiple risk factors.

If flucloxacillin is continued after cessation of ACUTEV, it is advisable to ensure that there are no signals of HAGMA, as there is a possibility of flucloxacillin maintaining the clinical picture of HAGMA (see **section 4.5**).

4.5 Interaction with other medicines and other forms of interaction:

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol as contained in ACUTEV with increased risk of bleeding; occasional doses have no significant effect.

The rate of absorption of paracetamol may be increased by metoclopramide or domperidone. Absorption of paracetamol may be reduced by cholestyramine.

Caution should be taken when ACUTEV is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see **section 4.4**).

Metabolism of paracetamol possibly accelerated by carbamazepine, fosphenytoin, phenytoin, phenobarbital, primidone (also isolated reports of hepatotoxicity).

Probenecid: Pre-treatment with probenecid can decrease paracetamol clearance and increase its plasma half-life and may thus increase the hepatoxicity of paracetamol. Although urinary excretion

of the sulphate and glucuronide conjugates of paracetamol are reduced, that of paracetamol is unchanged.

Antibacterials: The plasma-paracetamol concentrations considered an indication for antidote treatment should be halved in patients receiving enzyme inducing medicines such as rifampicin. Severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported in patients receiving isoniazid, alone or with other medicines for tuberculosis.

Antivirals: Severe hepatotoxicity has occurred after use of paracetamol in a patient taking zidovudine and co-trimoxazole. However, neither short-term nor long-term studies (the latter also in an individual patient) have shown any alteration of zidovudine elimination in patients taking zidovudine and paracetamol.
Paracetamol has also been found to enhance the antiviral effect of interferon alfa.

Chronic alcohol intake may increase the hepatotoxicity of paracetamol overdose. Acute alcohol intake may diminish an individual's ability to metabolise large doses of paracetamol, the plasma half-life of which can be prolonged.

4.6 Fertility, pregnancy and lactation:

Pregnancy:

Safety and efficacy in pregnancy have not been established.
Epidemiological studies on neurodevelopment in children exposed to paracetamol *in utero* showed indeterminate results. If used in pregnancy it should be used in the lowest effective dose for the shortest possible duration.

Breastfeeding:

Safety and efficacy in breastfeeding have not been established.

Paracetamol is excreted in breastmilk.

Fertility:

No data available.

4.7 Effects on ability to drive and use machines:

ACUTEV tablets have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects:

Tabulated list of adverse reactions:

Blood and lymphatic system disorders:	
Less frequent	Agranulocytosis, thrombocytopenia, leukopenia, pancytopenia, neutropenia, anaemia.
Immune system disorders:	
Less frequent	Anaphylaxis. Cutaneous hypersensitivity reactions including, among others, skin rashes and angioedema. Cases of serious skin reactions have been reported.
Frequency unknown	
Respiratory, thoracic and mediastinal disorders:	
Less frequent	Bronchospasm*.
Gastrointestinal disorders:	
Less frequent	Pancreatitis.
Hepato-biliary disorders:	
Less frequent	Hepatic dysfunction.

Skin and subcutaneous tissue disorders:	
Frequency unknown	Allergic dermatitis*. Hypersensitivity reactions including, among others, skin rashes. The rash is usually erythematous or urticarial but sometimes more serious and accompanied by fever and mucosal lesions. Stevens-Johnson syndrome, Toxic Epidermal Necrolysis, Acute Generalised Exanthematous Pustulosis (AGEP), Drug Rash with Eosinophilia and Systemic Symptoms (DRESS). Fixed Drug Eruptions (FDE) (see **section 4.4**), post-marketing.
Renal and urinary disorders:	
Less frequent	Renal colic, renal failure and sterile pyuria.
Metabolism and nutrition disorders:	
Frequency unknown	Pyroglutamic aciduria (5-oxoprolinuria) and high-anion gap metabolic acidosis**.

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

** Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see **section 4.4**). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

4.9 Overdose:

Prompt treatment is essential. In the event of an overdosage, consult a medical practitioner immediately, or take the person directly to a hospital. A delay in starting treatment may mean that antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed.

Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5 to 10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of medicines that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Mild symptoms during the first two days of acute poisoning, do not reflect the potential seriousness of the overdosage.

Liver damage may become apparent 12 to 48 hours or later after ingestion, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time. Liver damage may lead to encephalopathy, coma and death.

Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac dysrhythmias have been reported.

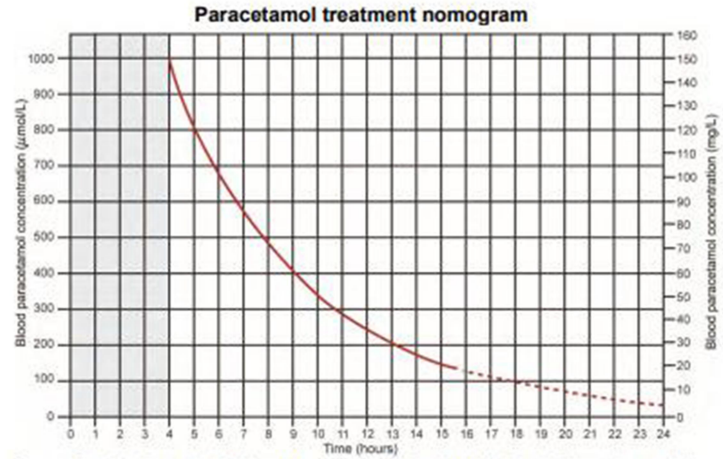
Treatment for paracetamol overdosage:

N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible, preferably within 8 hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken.

An initial dose of 150 mg/kg N-acetylcysteine in 200 ml dextrose injection, given intravenously over 15 minutes, followed by an intravenous infusion of 50 mg/kg in 500 ml dextrose injection over the next 4 hours and then 100 mg/kg in 1 000 ml dextrose injection over the next 16 hours. The volume of intravenous fluids should be modified for children.

Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg solution every four hours for 17 doses.

A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours unless high, may be misleading. Patients at risk of liver damage, and hence requiring continued treatment with N-acetylcysteine, can be identified according to their 4-hour plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the nomogram below. The nomogram should be used only in relation to a single acute ingestion.



Nomogram extracted from Essential Medicines Guideline, South African Department of Health, 2015.

Those whose plasma paracetamol levels are above the 'normal treatment line', should continue N-acetylcysteine treatment with 100 mg/kg IV over sixteen hours repeatedly until recovery. Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the 'high risk treatment line'. Prothrombin index correlates best with survival.

For overdose with an extended/modified release preparation the value of the nomogram is unknown. As there is no information on the plasma levels of paracetamol after an overdose of extended/modified release paracetamol preparations, all patients with suspected or known overdose with such preparations should receive N-acetylcysteine. Because of lack of data for extended/modified release formulations, a level below the 'treatment line' of the nomogram may not exclude the possibility of toxicity.

Monitor all patients with significant ingestions for at least ninety-six hours.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Category and class: A 2.7 Antipyretic or antipyretics and anti-inflammatory analgesics.

Pharmacotherapeutic group: Other analgesics and antipyretics.

ATC code: N02B E01

Mechanism of action:

Its mechanism of action is believed to include inhibition of prostaglandin synthesis, primarily within the central nervous system.

Clinical efficacy:

The perception of analgesia occurred from a median time of 15 minutes post dosing in adult patients after surgical removal of third molars with a paracetamol dose of 1 gram. The 1 gram dose demonstrated superior analgesia compared to the paracetamol 500 mg dose and placebo. Both paracetamol doses provided analgesia superior to placebo.

5.2 Pharmacokinetic properties:

Absorption:

Paracetamol tablets contain disintegrant excipient(s) which accelerates/improves the rate of disintegration/dissolution and absorption from the gastrointestinal tract and is distributed into most body tissues.

Human scintigraphy data demonstrate that paracetamol tablets with the disintegrant excipient(s) generally start to disintegrate by 5 minutes post dose.

Human pharmacokinetic data demonstrate that paracetamol can generally be detected in plasma by 10 minutes.

Human pharmacokinetic data demonstrate that early absorption of paracetamol (fraction of dose over the first 60 minutes) is 32 % greater from paracetamol tablets with disintegrant excipient(s). There is also less between-subject and less within-subject variability in early absorption of paracetamol from paracetamol tablets with the disintegrant excipient(s).

Human pharmacokinetic data demonstrate that maximum plasma concentration of paracetamol is reached at least 25 % faster for paracetamol tablets with the disintegrant excipient(s) in fasted and fed states.

Total extent of absorption of paracetamol from paracetamol tablets with the disintegrant excipient(s) is equivalent to that from immediate release paracetamol tablets.

Distribution:

Binding to plasma proteins is minimal at therapeutic concentrations.

The mean plasma half-life is about 2,3 hours and T_{max} is reached within 30 to 60 minutes.

Biotransformation and Elimination:

Paracetamol is metabolised in the liver and excreted in the urine mainly as glucuronide and sulphate metabolites - less than 5 % is excreted as unmodified paracetamol.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Tablet core:

Alginic acid

Calcium carbonate

Crospovidone Type B

Magnesium stearate

Povidone (K-25)

Starch, pregelatinised

Silica, colloidal anhydrous

Film-coating:

Aquarius Prime BDP118076 White

Calcium carbonate

Caprylic/Capric Trigliceride

De-oiled Sunflower Lecithin E322

Hypromellose 2910, 3 cp

Hypromellose 2910, 6 cp

Polydextrose

Polyethylene glycol 3 350

Polyethylene glycol 400

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

24 months.

6.4 Special precautions for storage:

Store at or below 25 °C.

Store in the original packaging until required for use.

6.5 Nature and contents of container:

ACUTEV is packaged in blister packs (PVC/PVdC-Aluminium or OPA/Alu/PVC-Aluminium). Blisters are packed in an outer carton.

Pack sizes:

The blisters are further packed into cardboard cartons containing 20 film-coated tablets.

6.6 Special precautions for disposal and other handling:

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City

Midrand

Gauteng

South Africa

2090

8. REGISTRATION NUMBER:

59/2.7/0652

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

2 June 2026

10. DATE OF REVISION OF THE TEXT: