Approved Professional Information for Medicines for Human Use:

ACTAMOL SOLUTION

SCHEDULING STATUS

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1. NAME OF THE MEDICINE

ACTAMOL SOLUTION 120 mg/5 mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ACTAMOL SOLUTION 120 mg/5 mL

Each 5 mL contains 120 mg paracetamol.

Each 5 mL contains 10,417 % *v/v* ethanol.

Each 5 mL contains 0,1 % *m/v* methylparaben (preservative).

Each 5 mL contains 0,05 % *m/v* propylparaben (preservative).

Contains no tartrazine.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution.

ACTAMOL SOLUTION 120 mg/5 mL

A clear, red solution with the odour and taste of cherry.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ACTAMOL is indicated for the symptomatic relief of mild to moderate pain and fever.

4.2 Posology and method of administration

Posology

DO NOT EXCEED THE RECOMMENDED DOSE.

Paediatric population

3 months to 1 year: 2,5 - 5 mL (60 – 120 mg).

1 to 5 years: 5 – 10 mL (120 – 240 mg).

6 to 12 years: 10 – 20 mL (240 – 480 mg).

May be given three to four times daily but with an interval of four hours between each dose.

DO NOT USE CONTINUOUSLY FOR LONGER THAN 10 (TEN) DAYS WITHOUT CONSULTING YOUR DOCTOR.

Method of administration

ACTAMOL is for oral administration.

4.3 Contraindications

- Hypersensitivity to the paracetamol or to any of the excipients listed in section 6.1.
- Sever liver function impairment.

4.4 Special warnings and precautions for use

This product 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.

- Dosages in excess of those recommended may cause severe liver damage.
- Consult your doctor if no relief is obtained with the recommended dosage or if pain or fever persists or gets worse at the recommended dosage, if new symptoms occur or if redness and swelling is present, as these could be signs of a more serious condition.
- Do not use continuously for longer than ten days without consulting your doctor.
- ACTAMOL should be given with care to patients with impaired kidney or liver function.
- Patients suffering from hepatitis or alcoholism, or recovering from any form of liver disease, should not take excessive quantities of ACTAMOL. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.
- Use ACTAMOL with caution in renal disease, alcohol dependence, chronic malnutrition or dehydration.
- Caution is advised if paracetamol, as in ACTAMOL, is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of

paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

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), eosinophilia and systemic (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 SCAR, treatment with ACTAMOL must immediately be discontinued and appropriate treatment instituted.

Paediatric population

Infants under three months: Not recommended.

4.5 Interaction with other medicines and other forms of interaction

- The hepatotoxicity of paracetamol, as in ACTAMOL, particularly after overdosage, may be increased by medicines which induce liver microsomal enzymes such as carbamazepine, barbiturates (e.g., phenobarbital), fosphenytoin, phenytoin, primidone, tricyclic antidepressants, and alcohol.
- Chronic alcohol intake can increase the hepatotoxicity of paracetamol overdose and may have contributed to the acute pancreatitis reported in one patient who had taken an overdose of paracetamol. Acute alcohol intake may diminish an individual's ability to metabolise large doses of paracetamol, the plasma half-life of which can be prolonged.
- Hepatotoxic medicines - increased risk of hepatotoxicity of paracetamol, as in ACTAMOL.

- Enzyme inducing medicines - increased risk of hepatotoxicity of paracetamol, as in ACTAMOL. Possible decrease in therapeutic effects of ACTAMOL.
- Metoclopramide - the speed of absorption of paracetamol, as in ACTAMOL, may be increased by metoclopramide.
- Cholestyramine – the absorption of paracetamol, as in ACTAMOL, is reduced if given within one hour of cholestyramine.
- Prolonged concurrent use of paracetamol, as in ACTAMOL, with salicylates increases the risk of adverse renal effects.
- Warfarin and anticoagulants - concurrent, chronic, high-dose administration of paracetamol, as in ACTAMOL, may increase the anticoagulant effect.
- Paracetamol, as in ACTAMOL, is recommended as the general analgesic and antipyretic of choice in patients on oral anticoagulant therapy. However, caution is needed since, although it has no effect on the gastric mucosa or on platelet function, some studies (with warfarin, anisindione, dicoumarol, or phenprocoumon) and isolated reports have found an increased risk of bleeding in patients taking regular doses of paracetamol while on an oral anticoagulant. An increase in INR has also been reported in controlled studies of the use of paracetamol in patients stabilised on warfarin. Increased monitoring of anticoagulant therapy may be appropriate for those also taking paracetamol, as in ACTAMOL, regularly.
- Antiepileptics: The plasma-paracetamol concentrations considered an indication for antidote treatment, should be halved in patients receiving enzyme inducing medicines such as carbamazepine, phenobarbital, phenytoin, or primidone.
- Probenecid: Pre-treatment with probenecid can decrease paracetamol clearance and increase its plasma half-life. 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, as in ACTAMOL, has also been found to enhance the antiviral effect of interferon alfa.
- The use of medicines that induce hepatic microsomal enzymes such as anticonvulsants and oral contraceptives may increase the extent of metabolism of paracetamol, as in ACTAMOL, resulting in reduced plasma concentrations of paracetamol and a faster elimination rate.
- Caution should be taken when paracetamol, as in ACTAMOL, is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risks factors (see section 4.4)

4.6 Fertility, pregnancy and lactation

The safety and efficacy of ACTAMOL in pregnancy and lactation have not been established.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

ACTAMOL has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

a) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with paracetamol.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Blood and lymphatic system disorders		Leucopenia, pancytopenia, neutropenia, anaemia	Blood disorder (including thrombocytopenia and agranulocytosis)[1]
Immune system disorders		Anaphylactic reaction, hypersensitivity	
Metabolism and nutrition disorders			Pyroglutamic aciduria (5-oxoprolinuria) and high-anion gap metabolic acidosis
Ear and labyrinth disorders			Hearing loss
Cardiac disorders			Possible increase in the risk of hypertension

Gastrointestinal disorders		Pancreatitis	Nausea and vomiting
Hepatobiliary disorders		Hepatitis	Liver injury[2, 6]
Skin and subcutaneous tissue disorders[5]		Rash, dermatitis, skin rashes, and other allergic reactions such as Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Acute Generalised Exanthematous Pustulosis (AGEP). The rash is usually erythematous or urticarial but sometimes more serious and accompanied by fever and mucosal lesions. More mild rashes and other hypersensitivity reactions also occur occasionally.	Risk of Fixed drug eruptions (FDE)*, Risk of Drug-induced hypersensitivity syndrome (DIHS)*, pruritic, urticaria

Renal and urinary disorders		Renal colic, renal failure and sterile pyuria, nephropathy toxic	Renal papillary necrosis[3]
General disorders and administration site conditions			Hypersensitivity reactions characterised by urticaria, dyspnoea, and hypotension.
Investigations			Transaminases increased[4]

[1] Reported following paracetamol use, but not necessarily causally related to paracetamol.

[2] Chronic hepatic necrosis has been reported in a patient who took daily therapeutic doses of paracetamol for about a year.

[3] Reported after prolonged administration.

[4] Low level transaminase elevations may occur in some patients taking therapeutic doses of paracetamol; these elevations are not accompanied with liver failure and usually resolve with continued therapy or discontinuation of paracetamol.

[5] Very rare cases of serious skin reactions have been reported.

[6] Chronic hepatic necrosis has been reported in a patient who took daily therapeutic doses of paracetamol for about a year and liver damage has been reported after daily ingestion of excessive amounts for shorter periods. A review of a group of patients with chronic active hepatitis failed to reveal differences in the abnormalities of liver function in those who were long-term users of paracetamol nor was the control of the disease improved after paracetamol withdrawal.

* Reported with post-marketing use of paracetamol.

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 professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za

4.9 Overdose

Prompt treatment is essential. In the event of an overdosage, consult a doctor 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 – 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

Symptoms of paracetamol overdosage in the first 24 hours include pallor, nausea, vomiting, anorexia, and possibly abdominal pain (see section 4.8). 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 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 arrhythmias have been reported.

Treatment for paracetamol overdosage:

N-acetylcysteine should be administered to all cases of suspected overdosage 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 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.**

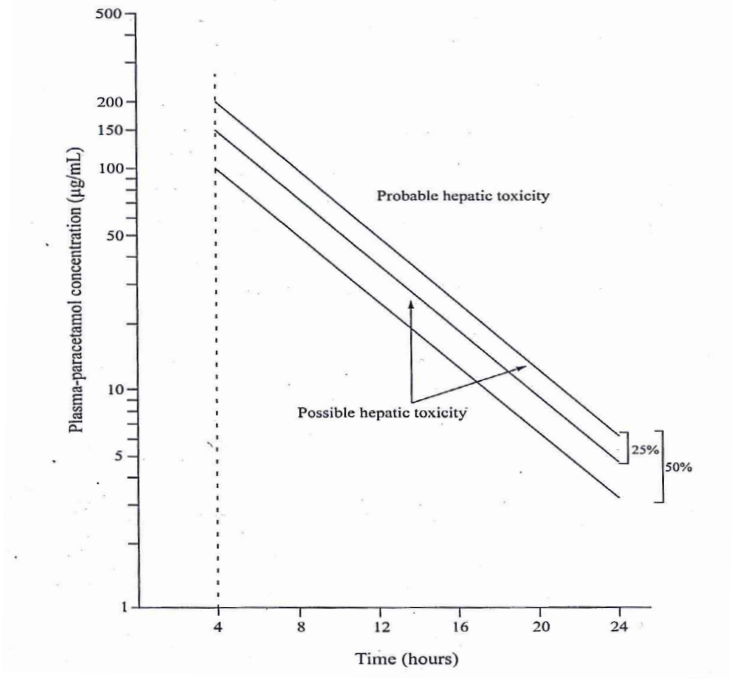
Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg every 4 hours for 17 doses.

A plasma paracetamol level should be determined 4 hours after ingestion in all cases of suspected overdosage. Levels done before 4 hours 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.

Those whose plasma paracetamol levels are above the “normal treatment line”, should continue N-acetylcysteine treatment with 100 mg/kg IV over 16 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.

Monitor all patients with significant ingestion for at least 96 hours.

Figure 1. A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion.



5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 2.8 Non-narcotic analgesics, antipyretics.

Pharmacotherapeutic group: Other Analgesics and Antipyretics (Anilides)

ATC Code: N02 BE01

Paracetamol has analgesic and antipyretic actions.

Paracetamol acts predominantly by inhibiting prostaglandin synthesis.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, paracetamol is well absorbed, with peak plasma concentrations obtained after 0,5 to 1 hour. The plasma half-life is about 2 hours.

Distribution

Plasma protein binding is variable. Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk.

Biotransformation & Elimination

Paracetamol is metabolised in the liver primarily by conjugation with glucuronic acid (about 60 %), sulphuric acid (about 35 %) and cysteine (about 3 %). Paracetamol is renally excreted primarily as conjugated metabolites.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol

Cherry essence no.1

Saccharin sodium

Carmoisine red (CI 14720)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a well-closed container protected from light at or below 25 °C.

Exposure to air should be minimum.

6.5 Nature and contents of container

ACTAMOL SOLUTION 120 mg/5 mL

Packed in 50 mL or 100 mL amber/white PVC or HDPE bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Shanur Healthcare (Pty) Ltd

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3A Eton Road, Parktown

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8. REGISTRATION NUMBER

ACTAMOL SOLUTION 120 mg/5 mL

Y/2.8/360

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 May 1992

10. DATE OF REVISION OF THE TEXT