PROFESSIONAL INFORMATION

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINAL PRODUCT

ACTATENSE (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ACTATENSE tablet contains

Paracetamol	450 mg
Doxylamine succinate	5 mg
Caffeine	30 mg
Codeine phosphate	10 mg

Also contains: Quinoline yellow CI 47005

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

A round yellow flat bevelled edge tablet, scored on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ACTATENSE tablets for adults are indicated for the symptomatic relief of mild to moderate pain and pain associated with tension and fever.

4.2 Posology and method of administration

Posology

Adults and children over 12 years: One or two tablets repeated four hourly if necessary. Do not exceed eight tablets per day. Consult your doctor if no relief is obtained with the recommended dosage.

Do not exceed the stated dose.

Special Populations

Elderly patients

The dosage should be reduced in elderly and debilitated patients (see section 4.4).

Impaired liver and kidney function

Patients suffering from liver or kidney disease should only take ACTATENSE under medical supervision.

The dosage in renal functional impairment must be reduced.

Paediatric population

ACTATENSE is contraindicated in children aged under 12 years (see section 4.3).

Method of administration

For oral administration without regard to food of drink intake.

Duration of administration

Do NOT use continuously for more than 10 days without consulting your doctor.

4.3 Contraindications

ACTATENSE is contraindicated in the following:

- known hypersensitivity to the active ingredients or any excipient of ACTATENSE listed in Section 6.1.
- severe liver function impairment.

- respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion.
- during an attack of bronchial asthma.
- heart failure secondary to lung disease.
- head injuries and conditions in which intracranial pressure is raised.
- the presence of acute alcoholism.
- after operations on the biliary tract.
- in patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment.
- in pregnancy and lactation as safety has not been established (see section 4.6).
- in children under the age of 12 years (see section 4.2 Paediatric population).

4.4 Special warnings and precautions for use

ACTATENSE 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.

Exceeding the prescribed dose, together with prolonged and continuous use of ACTATENSE, may lead to dependency and addiction.

Do not take concurrently with any other paracetamol or codeine containing products or alcohol.

Should be taken with caution by asthmatics (see section 4.3).

Special precautions

Paracetamol

Patients suffering from kidney or liver disease should take paracetamol under medical supervision.

It should be given with care in chronic malnutrition or dehydration.

Codeine phosphate

Codeine phosphate should be given with caution to patients with:

- hypothyroidism
- adrenocortical insufficiency
- impaired kidney or liver function
- myasthenia gravis
- prostatic hypertrophy
- shock
- inflammatory or obstructive bowel disorders.

Caffeine

Caffeine should be given with care to patients with:

- a history of peptic ulceration
- hyperthyroidism
- cardiac arrhythmias or other cardiovascular disease
- epilepsy, as these conditions may be exacerbated.

Doxylamine succinate

Doxylamine succinate has anticholinergic properties and should be used with care in conditions such as:

- glaucoma
- prostatic hypertrophy
- urinary retention
- pyloroduodenal obstruction.

ACTATENSE contains Quinoline Yellow CI 47005 which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic medicines or medicines that induce liver microsomal enzymes.

- Metoclopramide may accelerate the absorption of paracetamol.
- Probenecid may affect excretion and alter the plasma concentration.
- Cholestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol administration.
- Paracetamol must be given with caution if concomitantly used with antibacterial medicines (rifampicin; isoniazid; flucloxacillin), anticoagulants (warfarin), antiepileptic medicines (carbamazepine; phenobarbital; phenytoin; primidone) and antivirals (Interferon Alfa; zidovudine).

Codeine phosphate

Codeine's depressant effects are enhanced by:

- simultaneous intake of alcohol.
- other central nervous system depressants such as anaesthetics, hypnotics and sedatives and phenothiazines.

Quinidine can inhibit the analgesic effect of codeine.

Caffeine

Caffeine undergoes extensive metabolism by hepatic microsomal cytochrome P450 isoenzyme CYP1A2 and is subject to many interactions with other medicines and substances that enhance or reduce its metabolic clearance.

Caffeine should be given with care to patients concomitantly taking alcohol, antiarrhythmics

(mexiletine), antibacterials (ciprofloxacin; enoxacin; pipemidic acid), antidepressants (fluvoxamine), antiepileptics (phenytoin), antifungals (terbinafine), antigout medicines (allopurinol), gastrointestinal medicines (cimetidine), lithium, methoxsalen, sex hormones (oral contraceptives), sympathomimetics (phenylpropanolamine; ephedrine) and theophylline.

Doxylamine succinate

Doxylamine succinate may:

- enhance the effects of atropine and tricyclic antidepressants.
- mask the symptoms of damage caused by ototoxic medicine.
- affect the metabolism of medicine in the liver.
- enhance the sedative effect of central nervous system depressants including alcohol, barbiturates, hypnotics, narcotic analgesics, sedatives and tranquillisers.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety of ACTATENSE in pregnant women has not been established. ACTATENSE crosses the placenta.

Breastfeeding

Safety of ACTATENSE in lactating women has not been established. ACTATENSE is secreted in breast milk.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

ACTATENSE may lead to drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants.

Patients should be advised, particularly at the initiation of therapy, against taking charge of vehicles or machinery or performing potentially hazardous tasks where loss of concentration could lead to accidents.

4.8 Undesirable effects

a) Summary of the safety profile

ACTATENSE tablets have side effects.

Side effects of paracetamol are usually mild.

Dosages in excess of those recommended may cause severe liver damage (see section 4.4).

Exceeding the prescribed dose, together with prolonged and continuous use of ACTATENSE, may lead to dependency and addiction (see section 4.4).

b) Tabulated summary of the adverse effects

Frequencies have been evaluated according to the following convention:

Frequent = more frequent, very common and common.

Less frequent = single reports/isolated reports, uncommon, rare and very rare.

Frequency not known (no frequency data available).

MedDRA System Organ Classification (SOC) according to the sequence	**Adverse Reaction**	**Frequency per patient**
Paracetamol		
Blood and lymphatic system disorders	Thrombocytopenia, leukopenia, pancytopenia, neutropenia and agranulocytosis.	Less frequent
Immune system disorders	Allergic reactions, anaphylaxis.	Less frequent
Skin and subcutaneous tissue disorders	Mild rashes and hypersensitivity reactions, serious skin reactions,	Less frequent

	(Steven-Johnson syndrome, toxic epidermal necrolysis and acute generalised exanthematous pustulosis), angio-oedema.	
Gastrointestinal disorders	Pancreatitis.	Less frequent
Vascular disorders	Hypotension.	Less frequent
Respiratory disorders	Dyspnoea.	Less frequent
Doxylamine succinate		
Gastrointestinal disorders	Nausea, vomiting.	Frequent
	Dryness of the mouth, diarrhoea.	Less frequent
Ear and labyrinth disorders	Tinnitus.	Less frequent
Eye disorders	Blurred vision.	Less frequent
Psychiatric disorders	Sedation, nightmares, elation or depression, irritability, anorexia.	Less frequent
Renal and urinary disorders	Difficulty in micturition.	Less frequent
Nervous system disorders	Drowsiness.	Frequent
	Dizziness, insomnia, nervousness, tremors, muscle twitching, convulsions, tingling, headache, paraesthesia, epileptic fits.	Less frequent
Musculoskeletal and connective tissue disorders	Heaviness or weakness of the hands.	Less frequent
Cardiac disorders	Palpitations, tachycardia.	Less frequent
Respiratory, thoracic and mediastinal disorders	Bronchospasm.	Less frequent
Vascular disorders	Hypotension.	Less frequent

Skin and subcutaneous tissue disorders	Skin rashes, urticaria, purpura. Erythema multiforme, exfoliative bullous dermatitis, angio-oedema.	Less frequent
Renal and urinary disorders	Anuria.	Less frequent
Immune system disorders	Hypersensitivity reactions, allergy, anaphylaxis.	Less frequent
Blood and lymphatic system disorders	Blood dyscrasias, thrombocytopenia, leukopenia, agranulocytosis, eosinophilia, haemolytic anaemia.	Less frequent
Codeine phosphate		
Gastrointestinal disorders	Constipation.	Frequent
	Nausea, vomiting, dryness of the mouth.	Less frequent
Nervous system disorders	Drowsiness	Frequent
	Dizziness.	Less frequent
Psychiatric disorders	Confusion, restlessness, changes of mood, deepening of coma, euphoria.	Less frequent
Vascular disorders	Hypotension, orthostatic hypotension, facial flushing. Circulatory failure.	Less frequent
Cardiac disorders	Bradycardia, palpitations.	Less frequent
Skin and subcutaneous tissue disorders	Pruritus, urticaria, hyperhidrosis.	Less frequent
Renal and urinary disorders	Micturition, diuretic effect, ureteric spasms.	Less frequent
Hepatobiliary disorders	Biliary spasms.	Less frequent

Eye disorders	Miosis.	Less frequent
Ear and labyrinth disorders	Vertigo.	Less frequent
General disorders	Hyperthermia, raised intracranial pressure.	Less frequent
Caffeine		
Gastrointestinal disorders	Nausea.	Frequent
	Increased gastric secretion which may cause gastric ulceration.	Less frequent
Nervous system disorders	Dizziness, headache, muscle tremor.	Less frequent
Psychiatric disorders	Insomnia, irritability, anxiety, restlessness, excitement.	Less frequent
Ear and labyrinth disorders	Tinnitus.	Less frequent
Cardiac disorders	Tachycardia, extra systoles.	Less frequent
Eye disorders	Scintillating scotoma.	Less frequent

c) Description of selected adverse reactions

The prolonged use of high doses of codeine has produced dependence of the morphine type. Symptoms of restlessness and irritability may result when treatment is then stopped. Tolerance occurs rapidly to the stimulating effects of caffeine. Mild withdrawal syndrome has been reported by abruptly discontinuing (feelings of fatigue and sedation). With higher doses, headaches and nausea have been reported during withdrawal.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of ACTATENSE is important. It allows continued monitoring of the benefit/risk balance of ACTATENSE. Healthcare professionals are asked to report any suspected adverse reactions via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

Antihistamines (Doxylamine Succinate)

Overdosage of the doxylamine succinate causes sedation. Overdosage may be fatal, especially in infants and children in whom the main symptoms are central nervous stimulation and antimuscarinic effects, including ataxia, excitement, hallucinations, muscle tremor, convulsions, dilated pupils, dry mouth, flushed face and hyperpyrexia.

Deepening coma, cardiorespiratory collapse and death may occur within 18 hours. In adults the usual symptoms are central nervous depression with drowsiness, coma and convulsions. Hypotension may also occur. Treatment of antihistamine overdose is symptomatic and supportive.

Paracetamol

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 the 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 of paracetamol overdosage in the first 24 hours include pallor, nausea, vomiting, anorexia, and possibly 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 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

Although evidence is limited it is recommended that any adult person who has ingested about 5 – 10 grams or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding four hours should have the stomach emptied by emesis and a single dose of 50 g activated charcoal given via the lavage tube.

Ingestion of amounts of paracetamol smaller than this may require treatment in patients susceptible to paracetamol poisoning (see above). In patients who are stuporous or comatose endotracheal intubation should precede gastric lavage in order to avoid aspiration.

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 of N-acetylcysteine 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.

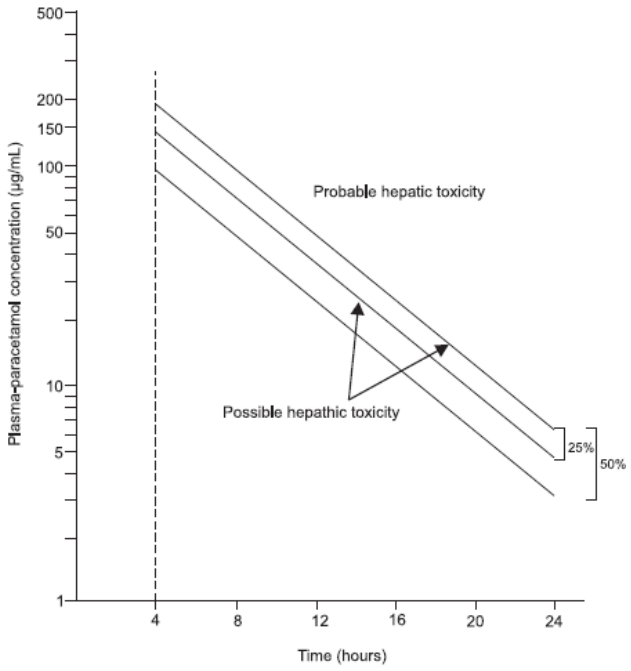
A plasma paracetamol level should be determined 4 hours after ingestion in all cases of suspected overdosage. Levels determined before 4 hours may be misleading. Patients at risk of liver damage, and hence requiring continued treatment with N-acetylcysteine, can be identified according to their 4-hour 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.

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 the lack of data for extended/modified release formulations, a level below the “treatment line” of the nomogram may not exclude the possibility of toxicity. Monitoring of all patients with significant ingestions for at least ninety six hours is recommended.

Paracetamol nomogram: A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion



Codeine Phosphate

Poisoning with codeine produces central stimulation with exhilaration and, in children, convulsions, followed by vomiting, drowsiness, respiratory depression, cyanosis and coma. Treatment is symptomatic and supportive.

Caffeine

Overdose of caffeine may produce nervousness, restlessness, insomnia, excitement, diuresis, facial flushing, muscle twitching, gastro-intestinal disturbance, tachycardia or cardiac arrhythmia, "rambling" flow of thought and speech, psychomotor agitation, or periods of inexhaustibility.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Medicine Class: A 2.8 Analgesic combinations

Pharmacotherapeutic group: Anilides, Paracetamol combinations

ATC Code: NO2B E51

ACTATENSE has analgesic, antipyretic and antihistaminic properties.

5.2 Pharmacokinetic properties

Paracetamol

Absorption:

It is readily absorbed from the gastrointestinal tract.

Distribution:

Peak plasma concentrations occur at about 30 to 60 minutes after oral doses.

Paracetamol is distributed into most body tissues. It crosses the placenta and is secreted in breast milk. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

Biotransformation:

It is metabolised predominantly in the liver. A minor hydroxylated metabolite (N-acetyl-p-benzoquinone-imine) which is usually produced in very small amounts by cytochrome P450 isoenzymes in the liver and kidneys. It is usually detoxified by conjugation with glutathione but may accumulate following paracetamol overdosage and cause tissue damage.

Elimination:

It is excreted in the urine mainly as the glucuronide and sulphate conjugates. The elimination half-life of paracetamol varies from about 1 to 3 hours.

Codeine phosphate

Absorption and Distribution:

Codeine phosphate is absorbed from the gastrointestinal tract. Ingestion of codeine phosphate produces peak plasma-codeine concentrations in about one hour. The plasma half-life has been

reported to be between 3 and 4 hours after an oral dose.

Biotransformation:

Codeine phosphate is metabolized by O- and N- demethylation in the liver to morphine, norcodeine.

Elimination:

Codeine phosphate and its metabolites are excreted almost entirely by the kidneys, mainly as conjugates with glucuronic acids.

Caffeine

Absorption:

It is absorbed readily after oral doses.

Distribution:

It is widely distributed throughout the body.

It passes readily into the CNS and into saliva; low concentrations are also present in breast milk and crosses the placenta.

Biotransformation:

In adults, it is metabolised almost completely in the liver via oxidation, demethylation, and acetylation.

Hepatic cytochrome P450 isoenzyme CYP1A2 is involved in enzymatic metabolism.

Its metabolism has been shown to be dose dependent with clearance decreasing as the dose is increased suggesting saturable metabolism.

Elimination:

It is excreted in the urine with only about 1 % unchanged.

Elimination half-lives are about 3 to 7 hours in adults.

Doxylamine succinate

Absorption:

It is absorbed from the gastrointestinal tract.

Distribution:

Peak plasma concentrations occur 2 to 3 hours after oral doses.

Elimination:

An elimination half-life of about 10 hours has been reported.

Excreted mainly by the kidneys.

5.3 Preclinical safety data

None stated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide , magnesium stearate, maize starch, microcrystalline cellulose, Povidone K25, Quinoline Yellow CI 47005, sodium starch glycolate and purified talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C and protect from light.

Do not remove the blister pack from the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Cardboard carton containing 20 or 40 tablets (2 or 4 aluminium/PVC blister packs of 10 tablets each).

6.6 Special precautions for disposal and other handling

ACTATENSE does not require any special storage conditions.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Smart Pharmaceuticals (Pty) Ltd

247 Voortrekker Road

Kraaifontein

Cape Town, 7570

8. REGISTRATION NUMBER

38/2.8/0152

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 May 2022

10. DATE OF REVISION OF THE TEXT

18 May 2022

ACT/PI/A