Professional Information for Colstat

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

Colstat hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains:

Paracetamol	300 mg
Ascorbic acid	75 mg
Caffeine	30 mg
Phenylephrine hydrochloride	5 mg
Chlorphenamine maleate	2 mg

For the full list of excipients, see section 6.1.

Sugar free.

3. PHARMACEUTICAL FORM

Hard capsules.

Size 0 hard gelatine capsule with a white body and light green cap.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Colstat is indicated for the symptomatic treatment and relief of colds and influenza.

4.2 Posology and method of administration

Posology

Adults: Two capsules three times daily.

Children 6 – 12 years: One capsule three times daily.

Not recommended for children under the age of 6 years.

Do not use continuously for more than 10 days without consulting a doctor.

DO NOT EXCEED THE RECOMMENDED DOSE.

Method of administration

Oral administration only.

4.3 Contraindications

- Hypersensitivity to paracetamol, ascorbic acid, caffeine, phenylephrine hydrochloride, chlorphenamine maleate or any of the other ingredients (see section 6.1).
- Severe hepatic impairment (Child Pugh C).
- Prostatic enlargement, paralytic ileus or pyloric stenosis.
- Closed angle glaucoma or with a narrow angle between the iris and the cornea.
- Epilepsy.
- Severe coronary disease, severe hypertension, cardiovascular disease.
- Hyperthyroidism.
- Pregnancy (see section 4.6).
- Patients being treated with monoamine oxidase inhibitors or within 10 days of stopping such treatment.
- Do not use in children under 6 years of age.

4.4 Special warnings and precautions for use

Colstat 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 use with any other paracetamol-containing products.

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

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.

Caffeine should be given with care to patients with a history of peptic.

Use with caution in conditions characterised by tachycardia such as thyrotoxicosis, cardiac insufficiency or failure, and in cardiac surgery.

Chlorphenamine maleate, in common with other medicines having anticholinergic effects, should be used with caution in patients with bronchitis, bronchiectasis and asthma; hepatic impairment or renal impairment.

Children and elderly patients are more likely to experience the neurological anticholinergic effects and paradoxical excitation (e.g. increased energy, restlessness, nervousness). Avoid use in elderly patients with confusion.

Consult your medical practitioner if no relief is obtained with the recommended dosage.

Use in children under 6 years of age:

Safety and efficacy have not been established (see section 4.2).

Porphyria:

Safety has not been established.

Severe cutaneous adverse reactions (SCARs):

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS) or 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, treatment with **Colstat** must immediately be discontinued and appropriate treatment instituted.

4.5 Interaction with other medicines and other forms of interaction

The rate 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. Excretion may be affected, and plasma concentrations of paracetamol altered when given with probenecid.

Ascorbic acid may increase the absorption of iron in iron-deficiency states. Omeprazole may affect the bioavailability of dietary vitamin C.

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.

The effects of phenylephrine hydrochloride are enhanced by guanethidine and to a lesser extent by reserpine, methyldopa and tricyclic antidepressants.

The antihistamine chlorphenamine maleate may enhance the sedative effect of central nervous system depressants including alcohol, barbiturates, hypnotics, narcotic analgesics, sedatives and tranquillisers and may produce a soothing effect in certain individuals.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established (see section 4.3).

4.7 Effects on ability to drive and use machines

The use of **Colstat** may lead to drowsiness and impaired concentration which may be aggravated by the simultaneous intake of alcohol and other central nervous system (CNS) depressants. Patients should be warned not to drive a motor vehicle, operate dangerous machinery, or climb dangerous heights as impaired decision making could lead to accidents.

4.8 Undesirable effects

Paracetamol:

Blood and lymphatic system disorders

Less frequent: thrombocytopenia, agranulocytosis, leucopenia, neutropenia, pancytopenia and anaemia

Immune system disorders

Less frequent: anaphylaxis, cutaneous hypersensitivity reactions including skin rash (the rash is usually erythematous or urticarial but sometimes more serious and may be accompanied by fever and mucosal lesions), angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis and acute generalised exanthematous

pustulosis

Respiratory, thoracic and mediastinal disorders

Less frequent: bronchospasm in patients sensitive to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs)

Gastrointestinal disorders

Frequency unknown: pancreatitis

Hepatobiliary disorders

Less frequent: hepatic dysfunction

Renal and urinary disorders

Frequency unknown: renal colic, renal failure and sterile pyuria

Phenylephrine hydrochloride:

Vascular disorders

Frequency unknown: undesirably high blood pressure with headache, palpitations and vomiting

Chlorphenamine maleate:

Blood and lymphatic system disorders

Frequency unknown: haemolytic anaemia, blood dyscrasias

Immune system disorders

Frequency unknown: allergic reaction, angioedema, anaphylactic reactions

Metabolism and nutritional disorders

Frequency unknown: anorexia

Psychiatric disorders

Frequency unknown: confusion*, excitation*, irritability*, nightmares*, depression

Nervous system disorders*

Frequent: sedation (varying from slight drowsiness to deep sleep), somnolence, disturbance in attention, abnormal coordination, dizziness, headache, incoordination, insomnia, tremors, convulsions

Eye disorders

Frequent: blurred vision

Ear and labyrinth disorders

Frequency unknown: tinnitus

Cardiac disorders

Frequency unknown: palpitations, tachycardia, dysrhythmias

Vascular disorders

Frequency unknown: hypotension

Respiratory, thoracic and mediastinal disorders

Frequency unknown: thickening of bronchial secretions

Gastrointestinal disorders

Frequent: nausea, dry mouth

Frequency unknown*:* vomiting, abdominal pain, diarrhoea, dyspepsia, constipation, colic and epigastric pain

Hepato-biliary disorders

Frequency unknown: hepatitis, including jaundice

Skin and subcutaneous disorders

Frequency unknown: exfoliative dermatitis, rash, urticaria, photosensitivity

Musculoskeletal and connective tissue disorders

Frequency unknown: muscle twitching, muscle weakness

Renal and urinary disorders

Frequency unknown*:* urinary retention

General disorders and administration site conditions

Frequent: fatigue

Frequency unknown: chest tightness.

*Children and elderly patients are more likely to experience the neurological anticholinergic effects and paradoxical excitation (e.g. increased energy, restlessness, nervousness).

Post-marketing experience

Paracetamol

Skin and subcutaneous disorders

Frequency unknown: severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of **Colstat** is important. It allows continued monitoring of the benefit/risk balance of **Colstat**. Health care providers 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

Paracetamol: Prompt treatment is essential. In the event of an overdosage, consult a doctor immediately, or take the person to a hospital directly. 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 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 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:

Although evidence is limited it is recommended that any adult person who has ingested 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 lavage (emesis may be adequate for children) 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.

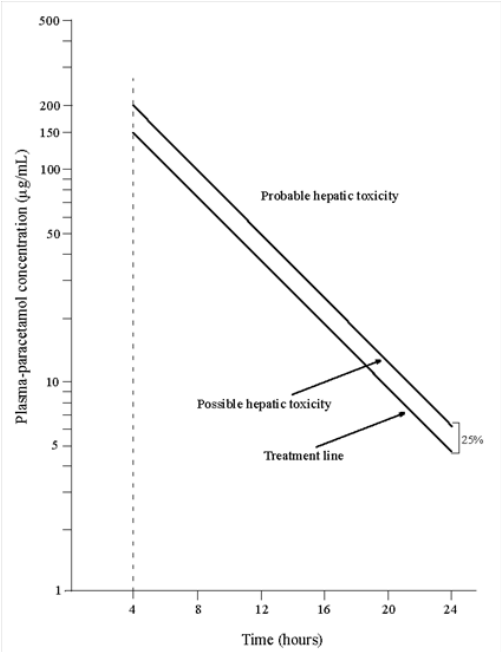
***N*-acetylcysteine** should be administered to all cases of suspected overdose as soon as possible preferably within eight hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken.

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

Orally: 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 4 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 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.



A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion (adapted from Rumack BH, Matthew HJ. Acetaminophen poisoning and toxicity. *Pediatrics* 1975; 55: 871–6).

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.

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

Ascorbic acid: Large doses are reported to cause diarrhoea and other gastrointestinal disturbances. It has also been stated that large doses may result in hyperoxaluria and the formation of renal calcium oxalate calculi and ascorbic acid should therefore be given with care to patients with hyperoxaluria.

Caffeine: Overdosage symptoms include restlessness, excitement, muscle tremor, tinnitus, scintillating scotoma, tachycardia and extrasystoles. Large doses caffeine can cause headache.

Phenylephrine hydrochloride: Tachycardia may occur with an overdose sufficient to stimulate the beta receptors of the heart. Mania has also followed the use of large oral doses of phenylephrine hydrochloride.

Chlorphenamine maleate: The estimated lethal dose of chlorphenamine is 25 – 50 mg/kg body mass. Symptoms and signs include sedation, paradoxical excitation of the CNS, toxic psychosis, convulsions, apnoea, anticholinergic effects, dystonic reactions and cardiovascular collapse including dysrhythmias.

Management should be as clinically indicated. Symptomatic and supportive measures should be provided with special attention to cardiac, respiratory, renal and hepatic functions and fluid and electrolyte balance. If overdosage is by the oral route, treatment with activated charcoal should be considered, provided there are no contraindications for use and the overdose has been taken recently (treatment is most effective if given within an hour of ingestion). Treat hypotension and dysrhythmias vigorously. CNS convulsions may be treated with IV diazepam. Haemoperfusion may be used in severe cases.

5. PHARMACOLOGICAL PROPERTIES

A 5.8 Preparations for the common cold including nasal decongestants

5.1 Pharmacodynamic properties

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

Ascorbic acid is vitamin C.

Caffeine is a mild stimulant.

Phenylephrine hydrochloride is a sympathomimetic agent.

Chlorphenamine maleate is a potent antihistamine (H_1-antagonist). Antihistamines diminish or

abolish the actions of histamine in the body by competitive reversible blockade of histamine H_1-receptor sites on tissues. Chlorphenamine also has anticholinergic activity. Antihistamines act to prevent the release of histamine, prostaglandins and leukotrienes and have been shown to prevent the migration of inflammatory mediators. The actions of chlorphenamine include inhibition of histamine on smooth muscle, capillary permeability and hence reduction of oedema and wheal in hypersensitivity reactions such as allergy and anaphylaxis.

5.2 Pharmacokinetic properties

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 paracetamol to plasma proteins is variable; 20 – 30 % may be bound at the concentrations encountered during acute intoxication. Following therapeutic doses 90 – 100 % of paracetamol 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.

Ascorbic acid is readily absorbed from the gastrointestinal tract and is widely distributed in the body tissues. Body stores of ascorbic acid normally are about 1,5 g. The concentration is higher in leucocytes and platelets than in erythrocytes and plasma. Ascorbic acid additional to the body's needs, generally amounts above 200 mg daily, is rapidly eliminated. Unmetabolised ascorbic acid and its inactive metabolic products are primarily excreted in the urine. The amount of ascorbic acid excreted unchanged in the urine is dose-dependent and may be accompanied by mild diuresis.

Caffeine is absorbed readily after oral doses. Maximum plasma concentrations are achieved within one hour and the plasma half-life is about 3,5 hours. 65 – 80 % of administered caffeine is excreted in the urine as 1-methyluric acid and 1-methylxanthine.

Phenylephrine hydrochloride is irregularly absorbed from the gastrointestinal tract and undergoes

first-pass metabolism by monoamine oxidase in the gut and liver. Orally administered phenylephrine thus has reduced bioavailability. It is excreted in the urine almost entirely as the sulphate conjugate.

Chlorphenamine maleate is well absorbed from the gastrointestinal tract, following oral administration. The effects develop within 30 minutes, are maximal within 1 to 2 hours and last 4 to 6 hours. The plasma half-life has been estimated to be 12 to 15 hours. Chlorphenamine is metabolised to the monodesmethyl and didesmethyl derivatives. About 22 % of an oral dose is excreted unchanged in the urine.

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dibasic calcium phosphate

Magnesium stearate

Liquid paraffin

Gelatine

Titanium dioxide (E171)

Brilliant blue FCF (E133)

Quinoline yellow (E104).

6.2 Incompatibilities

None reported.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Do not remove capsules from blister strips until required for use.

6.5 Nature and contents of container

Clear PVC/silver aluminium blister strips of 12 capsules in packs of 24 capsules in a unit carton.

6.6 Special precautions for disposal and other handling

Any unused medicine should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Lebasi Pharmaceuticals (Pty) Ltd

San Domenico Building, Unit 6

10 Church Street

Durbanville

7551

8. REGISTRATION NUMBER

C955 (Act 101/1965)

9. DATE OF FIRST AUTHORISATION

1970 (Act 101/1965)

10. DATE OF REVISION OF THE TEXT

21 June 2023