SCHEDULING STATUS:

S2

1. NAME OF THE MEDICINE:

COGESIC, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each tablet contains:

Paracetamol	500 mg
Codeine phosphate	8 mg

Preservative:

Sodium metabisulphite	0,081 % *m/m*

Contain sugar (sucrose)	20 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Flat blue tablet, scored on the one side.

Initial: 27/03//2024

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications

COGESIC tablets are indicated for the relief of mild to moderate pain and for the reduction of temperature in febrile conditions.

4.2 Posology and method of administration

Posology

DO NOT EXCEED THE RECOMMENDED DOSE.

Adults: One or two tablets every four to six hours.

Do not exceed an adult dose of 8 tablets per day

Children over 12 years: One tablet every four to six hours.

Children 6 to 12 years: Half to one tablet every six hours.

Do not use continuously for longer than five (5) days without consulting your doctor (see section 4.4).

Special populations

- The dosage should be reduced in elderly and debilitated patients.
- The administration of codeine during labour may cause respiratory depression in the newborn infant (see section 4.6).

Paediatric population

Not recommended for children under 6 years (see section 4.2).

Method of administration

For oral use.

Tablets must be swallowed with a sufficient quantity of liquid.

4.3 Contraindications

- Hypersensitivity to codeine phosphate or paracetamol or to any of the excipients in COGESIC (see section 6.1).
- Codeine is contraindicated in
    - respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion and after operations on the biliary tract;
    - in the presence of acute alcoholism, head injuries and conditions in which intracranial pressure is raised;
    - during an attack of bronchial asthma
    - or in heart failure secondary to lung disease.
- Patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment.

4.4 Special warnings and precautions for use

COGESIC 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.
- Do not use continuously for more than 5 days without consulting your doctor.
- Consult your doctor if no relief is obtained with the recommended dosage.
- Patients suffering from liver or kidney disease should take paracetamol under medical supervision.
- **Severe cutaneous adverse reactions (SCARs)**

  Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalized 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 COGESIC must immediately be discontinued and appropriate treatment instituted.

Codeine:

- **COGESIC contains codeine and exceeding the prescribed dose, together with prolonged and continuous use of this medication, may lead to dependency and addiction.**
- Codeine should be given with caution to patients with:
  - hypothyroidism,
  - adrenocortical insufficiency,

Initial: 27/03//2024

- myasthenia gravis,
- impaired renal function,
- impaired liver function,
- prostatic hypertrophy
- shock or
- inflammatory or obstructive bowel disorders.

- The dosage should be reduced in elderly and debilitated patients.
- The administration of codeine during labour may cause respiratory depression in the newborn infant (see section 4.6).

Paediatric population

Not recommended for children under 6 years (see section 4.2).

Excipients

Sugar

Contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take **COGESIC.**

4.5 Interaction with other medicines and other forms of interaction

May delay the absorption of other medicines administered concomitantly.

Paracetamol:

Initial: 27/03//2024

Hepatotoxic medicines - increased risk of hepatotoxicity.

Enzyme inducing medicines - increased risk of hepatotoxicity. Possible decrease in therapeutic effects of COGESIC.

Metoclopramide and domperidone - absorption of COGESIC may be accelerated.

Cholestyramine - absorption of COGESIC is reduced if given within one hour of cholestyramine.

Prolonged concurrent use of COGESIC with salicylates increases the risk of adverse renal effects.

Codeine

- Codeine is contraindicated in patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment (see section 4.3**).**
- The depressant effects of codeine are enhanced by depressants of the central nervous system such as:
    - alcohol,
    - anaesthetics,
    - hypnotics and sedatives,
    - phenothiazines and tricyclic antidepressants

4.6 Fertility, pregnancy and lactation

The administration of codeine during labour may cause respiratory depression in the newborn infant (see section 4.4).

Pregnancy

Codeine phosphate

A possible association with respiratory and cardiac malformations has been reported following first trimester exposure to codeine as contained in COGESIC.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

Administration during labour may depress respiration in the neonate. Opioid analgesics such as codeine, as contained in COGESIC, may cause gastric stasis during labour, increasing the risk of inhalation pneumonia in the mother.

Breastfeeding

Codeine phosphate

Administration to nursing women is not recommended as codeine phosphate may be secreted in breast milk and may cause respiratory depression in the infant.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

COGESIC may causes drowsiness.

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.

Initial: 27/03//2024

4.8 Undesirable effects

Tabulated list of adverse reactions

System Organ Class	Adverse reaction	Frequency
Blood and lymphatic system disorders	Agranulocytosis, Thrombocytopenia, Leukopenia, Pancytopenia, Neutropenia, Anaemia	Less frequent
Immune system disorders	Hypersensitivity reactions characterised by dyspnoea and orthostatic hypotension	Frequency unknown
Metabolism and nutrition disorders	Pyroglutamic aciduria (5-oxoprolinuria), High-anion gap metabolic acidosis,	Frequency unknown
Psychiatric disorders	Confusion, Restlessness	Frequent
	Euphoria, Changes of mood	Frequency unknown
Nervous system disorders	Drowsiness	Frequent
	Vertigo, Hypothermia, Raised intracranial pressure	Frequency unknown

	Deepening coma	
Eye disorders	Miosis	Frequency unknown
Cardiac disorders	Bradycardia, Palpitations	Frequency unknown
Vascular disorders	Orthostatic hypotension Hypotension Circulatory failure	Less frequent
Gastro-intestinal disorders:	Pancreatitis	Less frequent
	Nausea, Vomiting, Constipation, Dry mouth, Ureteric or biliary spasm	Frequency unknown
Hepato-biliary disorders	Hepatitis	Less frequent
Skin and subcutaneous tissue disorder	Skin rash, Dermatitis	Less frequent
	Urticaria Pruritis, Sweating, Facial flushing.	Frequency unknown
Musculoskeletal and connective tissue disorders	Muscle rigidity	Less frequent

Renal and urinary disorders	Renal colic, Renal failure, Sterile pyuria	Less frequent
	Nephropathy Difficulty on micturition	Frequency unknown
Post-marketing experience		
Gastro-intestinal disorders:	Increased risk of abdominal pain, including pancreatitis	Frequency unknown
Skin and subcutaneous tissue disorders	Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), eosinophilia and systemic (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE)	Frequency unknown

Paracetamol

System Organ Class	Adverse reaction	Frequency
Blood and lymphatic system disorders	Haematological reactions e.g. Agranulocytosis, Thrombocytopenia, Leukopenia,	Less frequent

	Pancytopenia, Neutropenia, Anaemia	
Gastro-intestinal disorders:	Pancreatitis	Less frequent
Hepato-biliary disorders	Hepatitis	Less frequent
Skin and subcutaneous tissue disorder	Skin eruptions, rash, erythematous or urticarial*	Less frequent
Renal and urinary disorders	Renal colic, Nephropathy, Renal failure, Sterile pyuria	Less frequent
Post-marketing experience		
Blood and lymphatic system disorders	Agranulocytosis, thrombocytopenia	Less frequent
Immune system disorders	Anaphylaxis, cutaneous hypersensitivity reactions including, among others, skin rashes and angioedema. Very rare cases of serious skin reactions have been reported.	Less frequent
Respiratory, thoracic and mediastinal disorders	Bronchospasm**	Less frequent
Hepatobiliary	Hepatic dysfunction	Less frequent

Initial: 27/03//2024

disorders		
Skin and subcutaneous tissue disorders	Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), eosinophilia and systemic (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE)	Frequency unknown

* Skin eruptions have occurred. Sensitivity reactions including skin rash may occur. This is usually erythematous or urticaria! but sometimes may be more serious and may be accompanied by drug fever and mucosal lesions.

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

Codeine phosphate

System Organ Class	Adverse reaction	Frequency
Immune system disorders	Dose-related histamine-releasing effect, allergic reactions such as urticarial and pruritus as well as hypotension and flushing, hypersensitivity syndrome as part of a	Frequency unknown

	maculopapular rash, fever, splenomegaly, and lymphadenopathy	
Endocrine disorders	Hyperglycaemia	Frequency unknown
Metabolism and nutrition disorders	Anorexia	Frequency unknown
Psychiatric disorders	Confusion	Frequent
	Restlessness*, mood changes*	Less frequent
	Excitement, euphoria, mental depression, hallucinations and nightmares, and dysphoria.	Frequency unknown
Nervous system disorders	Dizziness, drowsiness	Frequent
	Faintness*, sedation*, vertigo*	Less frequent
	Headache, raised intracranial pressure, convulsions	Frequency unknown
Eye disorders	Miosis*	Less frequent
	Blurred or double vision or other changes in vision	Frequency unknown

Cardiac disorders	Bradycardia, palpitations*	Less frequent
	Tachycardia	Frequency unknown
Vascular disorders	Postural hypotension	Frequency unknown
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Frequency unknown
Gastro-intestinal disorders:	Nausea, vomiting, constipation,	Frequent
	Dry mouth*	Less frequent
	Stomach cramps, pancreatitis	Frequency unknown
Hepato-biliary disorders	Biliary spasm	Frequency unknown
Skin and subcutaneous tissue disorder	Facial flushing	Frequent
	Sweating	Less frequent
	Allergic reactions such as skin rashes, urticaria, pruritus,	Frequency unknown
Musculoskeletal and connective tissue disorders	Muscle rigidity, uncontrolled muscle movements	Frequency unknown

Renal and urinary disorders	Urinary retention, ureteric spasm, antidiuretic effect, difficulty with micturition, dysuria	Frequency unknown
Reproductive system and breast disorders	Sexual dysfunction, erectile dysfunction, decreased potency, decreased libido	Frequency unknown
General disorders and administrative site conditions	Drug withdrawal syndrome	Less frequent
	Hypothermia, malaise, tiredness and facial oedema	Frequency unknown

*These effects occur more commonly in ambulant patients than in those at rest in bed and in those without severe pain.

These are less common than with morphine.

Codeine may cause respiratory depression, circulatory failure, hypotension, orthostatic hypotension, deepening coma with larger doses.

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 asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Medicine 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 medical practitioner 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 drugs 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.

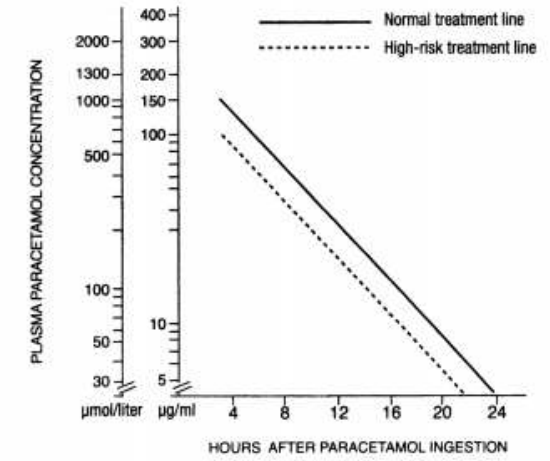
Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac dysrhythmias have been reported.

Treatment for paracetamol overdosage:

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. 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 four hours, and then 100 mg/kg in 1000 mL dextrose injection over the next sixteen hours. **The volume of intravenous fluid 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 four hours for seventeen 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.



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

Initial: 27/03//2024

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.

The latest information regarding the treatment of overdosage can be obtained from your nearest poison centre.

Codeine:

Symptoms include restlessness, excitement, respiratory depression and hypotension with circulatory failure and coma. In children convulsions may occur. The specific antagonist, naloxone hydrochloride is used to counteract the severe respiratory depression.

In the event of overdosage, consult a doctor or take the patient to the nearest hospital immediately.

Treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.8 Analgesic Combinations

ATC Code: N02AJ06

COGESIC tablets have analgesic and antipyretic action.

5.2 Pharmacokinetic properties

Paracetamol

Absorption:

Following oral administration, paracetamol is well absorbed, with peak plasma concentrations obtained after 0, 5 to 1 hour.

Distribution:

Once absorbed, the plasma half-life is about 2 hours.

Plasma protein binding is variable.

Metabolism:

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

Elimination:

Paracetamol is renally excreted primarily as conjugated metabolites.

Codeine

Once absorbed, codeine is metabolized by the liver. Codeine's metabolites are excreted chiefly as inactive forms in the urine. A small fraction, approximately 10% of administered codeine is 0-demethylated to morphine, and free and conjugated morphine can be found in the urine after therapeutic doses of codeine. The half-life of codeine in plasma is 2-4 hours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin,

Indigo Carmine Lake E 132 IH (CI 73015:1),

povidone,

magnesium stearate,

maize starch,

modified starch,

powdered sucrose.

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 strong light in a well-closed container. Protect from moisture. Exposure to air should be minimal.

6.5 Nature and contents of container

Cartons containing 2 x 10 tablets in push through blister packs.

White plastic (LDPE) Ziploc bag (Patient Ready Pack) containing 56 tablets.

Initial: 27/03//2024

Amber plastic (PVC) bottles containing 100, 500, and 1 000 tablets.

White plastic (HDPE) bottles containing 1 000 tablets.

Blue / green plastic buckets containing 5 000 tablets.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Oethmaan Biosims (Pty) Ltd

207A Sherwood House

Greenacres Office Park

c/o Victory and Rustenburg Roads

Victory Park

Johannesburg

2195

8 REGISTRATION NUMBER(S):

X/2.8/109

Initial: 27/03//2024

9 DATE OF FIRST AUTHORISATION

23 August 1989

10 DATE OF REVISION OF THE TEXT

27 March 2024

Initial: 27/03//2024