SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

SYNALEVE CAPSULES, 200 mg/8 mg/400 mg, capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

Meprobamate 200 mg

Codeine phosphate 8 mg

Paracetamol 400 mg

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules.

SYNALEVE CAPSULES: Size ‘0' and/or ‘0E’, elongated, hard gelatin capsule with powder blue, opaque cap and ivory, opaque body with "SYNALEVE" imprinted on both the cap and the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Relief of pain and pain associated with tension.

4.2 Posology and method of administration

Posology

DO NOT EXCEED THE RECOMMENDED DOSE.

Adults and children over the age of 12 years:

One or two (1 or 2) capsules three to four (3 to 4) times a day, if necessary.

Do not exceed eight (8) capsules per day.

Method of administration

For oral administration.

4.3 Contraindications

- Hypersensitivity to meprobamate, codeine phosphate and/or paracetamol, or to any of the excipients listed in section 6.1.
- Patients with impaired liver or kidney function.
- Patients with respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion, after operations on the biliary tract, acute alcoholism, head injuries and conditions in which intracranial pressure is raised. It should not be given during an attack of bronchial asthma or in heart failure secondary to chronic lung disease.
- Patients with acute intermittent porphyria.
- Patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment (see section 4.5).
- During third trimester of pregnancy (see section 4.6).
- In women who are breastfeeding (see section 4.6).
- Children under the age of 12 years.

- Children (0 to 18 years of age) who undergo tonsillectomy or adenoidectomy surgery for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see section 4.4).

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.

Paracetamol:

- 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), Stevens-Johnson syndrome (SJS), acute generalized 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 SCAR, treatment with SYNALEVE CAPSULES must immediately be discontinued and appropriate treatment instituted (see section 4.8).

Codeine:

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, impaired liver function, prostatic hypertrophy or shock.
- It should be used with caution in patients with inflammatory or obstructive bowel disorders.
- The dosage should be reduced in elderly and debilitated patients.
- The prolonged use of codeine has produced dependence of the morphine type.
- *Opioid use disorder (abuse and dependence)*

  Tolerance, physical and psychological dependence and opioid use disorder (OUD) may develop upon repeated administration of opioids such as codeine. Abuse or intentional misuse of SYNALEVE CAPSULES may result in overdose and/or death.

  Patients should be informed about the risks and signs of OUD as well as serious clinical outcomes. If these signs occur, patients should be advised to contact their doctor.

  Withdrawal symptoms, such as restlessness and irritability may occur once the medicine is stopped.

  Increased risk of addiction in patients with personal or family history of substance abuse or mental health disorders.
- *Opioid-induced Hyperalgesia (OIH)*

  Opioid pain medicines have been associated with opioid-induced hyperalgesia (OIH), a condition where opioids cause an increase in pain (called hyperalgesia) or an increased sensitivity to pain (called allodynia). Increases in pain typically occur following a dose increase and resolve quickly following proper diagnosis and management of the condition. Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia).

Meprobamate:

- Withdrawal of meprobamate from patients who have been receiving it in high dosage or for prolonged periods of time should be gradual.
- Meprobamate may induce the hepatic microsomal enzymes involved in drug metabolism.
- Although meprobamate has anticonvulsant properties, it may induce convulsions in patients with a history of epilepsy.
- Administer cautiously to pre-psychotic individuals who may form a dependence on meprobamate and codeine phosphate.
- Consult your doctor if no relief is obtained with the recommended dose.
- Dosages in excess of those recommended may cause severe liver damage.
- Do not use continuously for longer than ten days without consulting your doctor.

Paediatric population

SYNALEVE CAPSULES is contraindicated in children under 12 years of age (see section 4.2 & section 4.3).

Children with compromised respiratory function:

Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

4.5 Interactions with other medicines and other forms of interaction

- Contraindicated in patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment (see section 4.3).

- The use of this medicine may lead to drowsiness and impaired concentration, that may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants.
- The depressant effects of codeine are enhanced by depressants of the central nervous system such as alcohol, anaesthetics, hypnotics, sedatives and phenothiazines.
- Meprobamate may lower the tolerance to alcohol and other depressants of the central nervous system.

Additional information on special populations

No information available.

Paediatric population

No information available.

4.6 Fertility, pregnancy and lactation

Pregnancy

SYNALEVE CAPSULES is not recommended for use by women in early pregnancy, and is contraindicated in the third trimester of pregnancy (see section 4.3).

Breastfeeding

SYNALEVE CAPSULES is contraindicated in breastfeeding women (see section 4.3).

Fertility

No data on male and female fertility is available.

4.7 Effects on ability to drive and use machines

This medicine may lead to drowsiness and impaired concentration and patients should not drive vehicles or operate machines where loss of attention could lead to accidents.

4.8 Undesirable effects

The following adverse reactions are presented according to the MedDRA system organ classification. Frequency cannot be estimated from the available data.

a. Summary of the safety profile

No information available.

b. Tabulated list of adverse reactions

Paracetamol		
SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Immune system disorders	Frequency unknown	Sensitivity reactions resulting in reversible skin rash or blood disorders may occur. Drug-induced hypersensitivity syndrome (DIHS), hypersensitivity reactions characterised by urticaria, dyspnoea, and hypotension (see section 4.4).
Skin and subcutaneous tissue disorders	Frequency unknown	Fixed drug eruptions** (FDE) (see section 4.4)

Codeine		
SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Immune system disorders	Frequency unknown	Reactions such as urticaria and pruritus may occur.
Psychiatric disorders	Frequency unknown	Restlessness, changes in mood.
Nervous system disorders	Frequency unknown	Drowsiness, raised intracranial pressure may occur.
Eye disorders	Frequency unknown	Miosis.
Cardiac disorders	Frequency unknown	Palpitations.
Vascular disorders	Frequency unknown	Orthostatic hypotension.
Gastrointestinal disorders	Less frequent	Acute pancreatitis***
	Frequency unknown	Nausea, vomiting, constipation.
Renal and urinary disorders	Frequency unknown	Micturition may be difficult and there may be ureteric or biliary spasm.
General disorders and administration site conditions	Frequency unknown	Hypothermia.
Meprobamate		
SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Blood and lymphatic system disorders	Frequency unknown	Blood disorders including agranulocytosis, eosinophilia, leucopenia, thrombocytopenia and aplastic anaemia have occasionally been reported.

Immune system disorders	Frequency unknown	Hypersensitivity reactions occur occasionally. These may be limited to skin rashes, urticaria and purpura or may be more severe with angioneurotic oedema, bronchospasm or anuria. Symptoms of porphyria may be exacerbated.
Nervous system disorders	Frequency unknown	Paraesthesia, weakness and other central effects such as headache, excitement, dizziness, ataxia and disturbances of vision.
Cardiac disorders	Frequency unknown	Tachycardia and cardiac dysrhythmias.
Vascular disorders	Frequency unknown	Hypotension.
Gastrointestinal disorders	Frequency unknown	Nausea, vomiting, diarrhoea.
Skin and subcutaneous tissue disorders	Frequency unknown	Erythema multiforme has been reported.

Post marketing experience

The following side effects have been reported and frequencies are unknown:

**Fixed drug eruptions (FDE) and drug-induced hypersensitivity syndrome (DIHS) (see section 4.4).

*** Less frequent increased risk of abdominal pain, including pancreatitis has been reported.

c. Description of selected adverse reactions

Sensitivity reactions resulting in reversible skin rash or blood disorders may occur. Treatment should be discontinued as soon as these hypersensitivity reactions occur. Post marketing

data for paracetamol, as contained in SYNALEVE CAPSULES, has reported Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) as an undesirable effect with unknown frequency (see section 4.4). Post marketing data for codeine, as contained in SYNALEVE CAPSULES, has reported increased risk of abdominal pain, including pancreatitis as an undesirable effect with unknown frequency.

d. Paediatric population

Frequency, type and severity of adverse reactions in children over the age of 12 years are expected to be the same as in adults.

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. Health care 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 SAHPRA website.

For reporting of side effects directly to the HCR, contact +27 11 635 0134 or email Adcock.aereports@adcock.com.

4.9 Overdose

SYNALEVE CAPSULES contain 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 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 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 1 000 mL dextrose injection over the next sixteen hours. **The volume of intravenous fluid should be modified for children.**

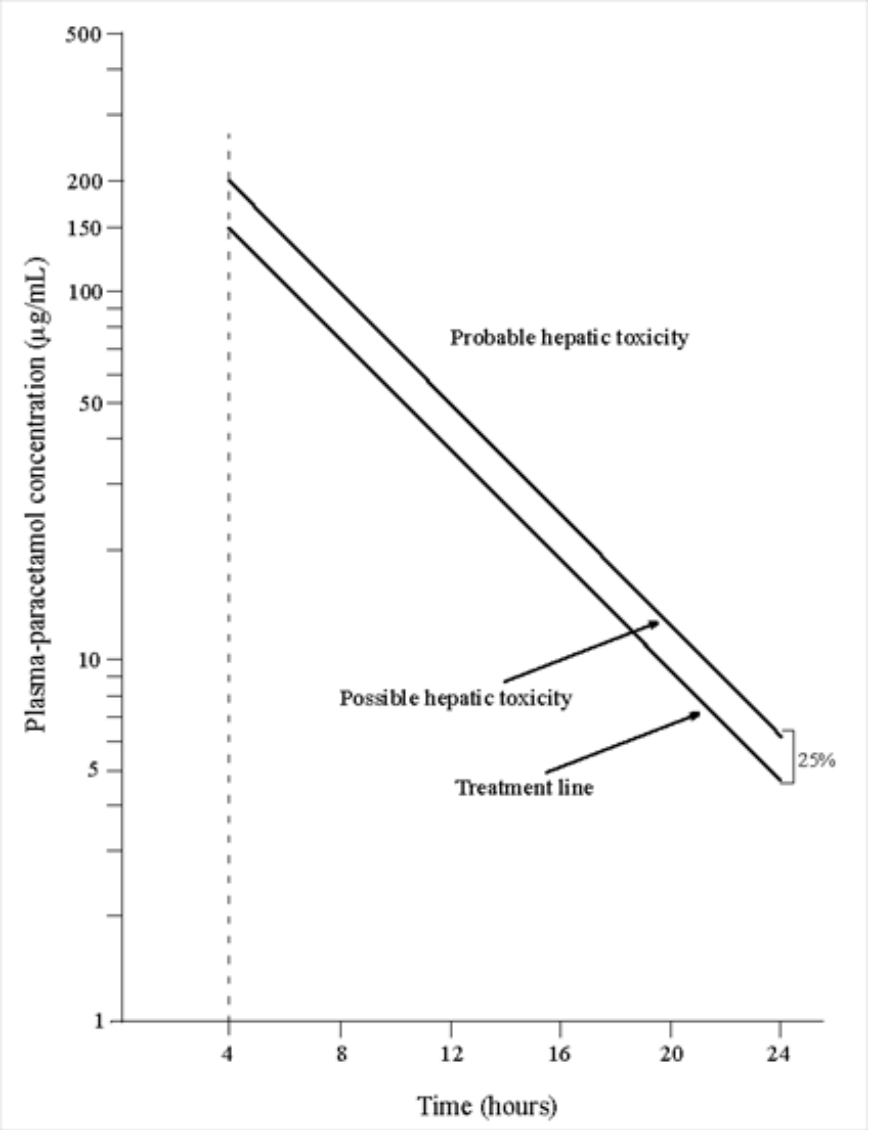
Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg every four hours for seventeen doses.

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

A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion (Reference: Martindale).



Codeine phosphate overdosage symptoms result in CNS stimulation, a feeling of exhilaration and then convulsions, nausea and vomiting, contracted pupils, increased pulse, respiratory depression and coma.

Acute meprobamate overdosage can produce stupor, coma, convulsions, shock, circulatory and respiratory collapse.

In the event of overdosage consult a doctor or take the patient to the nearest hospital immediately. Specialised treatment is essential as soon as possible.
The latest information regarding the treatment of overdosage can be obtained from the nearest poison centre.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 2.8 Analgesic combinations.

SYNALEVE CAPSULES combines the analgesic action of paracetamol and codeine phosphate with the tranquilising and skeletal muscle relaxing properties of meprobamate.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill

Purified talc

Capsule body

Erythrosin Cl 45430

Gelatin

Titanium Dioxide Cl 77891

Quinoline Yellow Cl 47005

Capsule cap

Gelatin

Indigo Carmine Cl 73015

Titanium Dioxide Cl 77891

Constituents of the black printing ink on capsule

Opacode Black S-1-27794:

Industrial Methylated Spirit 74 OP

Iron Oxide Black (CI # 77499)

Isopropyl Alcohol

N-Butyl Alcohol

Propylene Glycol

Purified Water

Shellac Glaze-47,5 % (22 % Esterified) in IMS 74 OP

Or

TekPrint SW-9008 Black Ink:

Black Iron Oxide E172

Butyl Alcohol

Dehydrated Alcohol

Isopropyl Alcohol

Potassium Hydroxide

Propylene Glycol

Purified Water

Shellac

Strong Ammonia Solution

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

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

Protect from light.

6.5 Nature and contents of container

Blister packs of 20, 40 and 100 capsules.

Containers of 100 and 500 capsules.

Capsules packed in 20’s:

20’s (2 X 10) Blister pack using aluminium foil and clear PVC Cello.

Capsules packed in 40’s:

40’s (4 X 10) Blister pack using PVC film and printed aluminium foil.

Capsules packed in 100’s:

- 100’s Securitainer with closure and wadding foam.
- 100’s White cylindrical screw type HDPE container with screw cap.
- 100’s (10 X 10) Blister pack with PVC film and printed aluminium foil.

Capsules packed in 500’s:

- 500’s White PVC Jar with an HDPE screw cap and foam insert.

Not all pack types and pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand, 1685

Customer care: 0860 ADCOCK/232625

8. REGISTRATION NUMBER(S)

B/2.8/80

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09 January 1970

10. DATE OF REVISION OF THE TEXT

10 October 2025