PACKAGE INSERT

SCHEDULING STATUS

Schedule 2

PROPRIETARY NAME AND DOSAGE FORM

SINUMAX® WITH CODEINE tablets

COMPOSITION

Each tablet contains the following active ingredients: 500 mg paracetamol, 30 mg pseudoephedrine hydrochloride and 8 mg codeine phosphate.

Inactive ingredients: magnesium stearate, microcrystalline cellulose (Avicel), pregelatinised starch, sodium starch glycolate,

Sugar free

PHARMACOLOGICAL CLASSIFICATION

A. 5.8 Preparations for the common cold including nasal decongestants and antihistaminics.

PHARMACOLOGICAL ACTION

SINUMAX WITH CODEINE contains paracetamol, pseudoephedrine hydrochloride and codeine phosphate.

Paracetamol has analgesic and antipyretic effects. Pseudoephedrine relieves nasal congestion.

Codeine phosphate has analgesic effects.

INDICATIONS

For the symptomatic relief of nasal, sinus and Eustachian tube mucal congestion in the presence of mild to moderate pain and fever due to colds and influenza.

CONTRAINDICATIONS

Do not use this product if you are allergic or have a hypersensitivity to any of the ingredients.

This product should not be used by patients being treated with monoamine oxidase inhibitors (MAOIs), or within two weeks of stopping treatment with these medications. The concomitant use of pseudoephedrine and MAOIs may cause a rise in blood pressure or hypertensive crisis.

Paracetamol should not be used in patients with severe liver disease.

Pseudoephedrine should not be used in patients suffering from any of the following: heart disease (especially coronary insufficiency or dysrhythmias), high blood pressure (hypertension), an overactive thyroid gland (hyperthyroidism), tumour of the adrenal gland (phaeochromocytoma) and raised intraocular pressure (closed-angle glaucoma).

Pseudoephedrine should be avoided in patients receiving chloroform, cyclopropane, halothane or other halogenated anaesthetics.

Codeine should not be used during an attack of bronchial asthma or in patients with heart failure as a result of lung disease and should be avoided by patients with abnormally slow and/or shallow breathing, especially in the presence of bluish discolouration of skin due to lack of oxygen and excessive bronchial secretion and after operations on the biliary tract; in the presence of acute alcoholism, head injuries and conditions in which the pressure inside the skull is raised.

SINUMAX WITH CODEINE is contraindicated under 12 years of age for pain.

SINUMAX WITH CODEINE is contraindicated for pain management following tonsillectomy and/or adenoidectomy in children under 18 years of age.

In CYP2D6 ultra-rapid metabolisers who convert codeine into its active metabolite more rapidly and completely than other people. These individuals may experience signs of overdose/toxicity including symptoms such as extreme sleepiness, confusion or shallow breathing which may be life threatening (see WARNINGS and SPECIAL PRECAUTIONS and KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT).

SINUMAX WITH CODEINE is contraindicated in breastfeeding mothers (see HUMAN REPRODUCTION).

WARNINGS AND SPECIAL PRECAUTIONS

Paracetamol

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.

Taking more than the recommended dose may cause severe liver damage.

Patients suffering from liver or kidney disease should take paracetamol only if instructed to do so by the doctor.

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

Do not use continuously for longer than 5 days without consulting your doctor.

If pain or fever persists or gets worse, or if new symptoms occur, a medical practitioner should be consulted.

Serious skin reactions such as acute generalised exanthematous pustulosis (AGEP), Stevens - Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), have been reported very rarely in patients receiving paracetamol. Patients should be informed about the signs of serious skin reactions, and use of this medicine should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Alcohol warning: Chronic alcohol users should ask their doctors whether they should take paracetamol or other pain relievers or fever reducers.

Do not use with any other medicines containing paracetamol.

Codeine

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

Use of SINUMAX WITH CODEINE is not recommended in adolescents 12 to under 18 years of age for pain.

Ultra Rapid Metabolisers of Codeine

Some individuals may be ultra-rapid metabolisers due to a specific CYP2D6*2x2 genotype. These individuals convert codeine into the active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at the recommended dosage regimen for SINUMAX WITH CODEINE, individuals who are ultra-rapid metabolisers may have life-threatening or fatal respiratory depression or experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing. Respiratory depression and death have occurred in children who received codeine in the postoperative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolisers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Children who are ultra-rapid metabolisers of codeine with obstructive sleep apnoea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to the respiratory depressant effects of codeine. Codeine-containing medicines are contraindicated in CYP2D6 ultra-rapid metabolisers (see CONTRAINDICATIONS).

The prevalence of this CYP2D6 phenotype may vary between ethnic groups.

Patients should take the lowest effective dose for the shortest period of time. Patients should be informed about these risks and the signs of morphine overdose (see KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT)

Codeine should be given with caution to patients with an underactive thyroid or adrenal gland (hypothyroidism, adrenal insufficiency), myasthenia gravis or impaired kidney or liver function, enlargement of prostate gland (prostatic hypertrophy) or shock. It should be used with care in patients with inflamed or obstructive bowel disease and in patients at risk of paralytic ileus. The dosage should be reduced in elderly patients.

Do not use with alcohol. A doctor or pharmacist should be consulted before use if a patient is taking benzodiazepines or other sedatives. Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedations, respiratory depression, coma, and death (see INTERACTIONS).

The depressant effects of codeine are enhanced by medicines which slow down the action of the central nervous system (CNS) such as alcohol, anaesthetics, hypnotics and sedatives, phenothiazines and tricyclic antidepressants.

Codeine should be used with caution in patients with convulsive disorders, head injuries, and in conditions in which intracranial pressure is raised.

Codeine is an opioid medicine and carries the risk of misuse and abuse. Tolerance, psychological and / or physical dependence and addiction may occur with prolonged use and/or high doses of codeine (see SIDE EFFECTS).

Codeine may cause abnormally slow and/or shallow breathing in the newborn infant if given during labour.

Codeine should be used with caution in patients with compromised respiratory function, such as bronchial asthma, pulmonary oedema, obstructive airways disease, acute respiratory depression, severe lung disease, obesity, obstructive sleep apnoea, or obstructive bowel disorders and in patients at risk of paralytic ileus.

Therapy should be stopped at the earliest sign of abdominal pain or trouble breathing.

Use of SINUMAX WITH CODEINE should be discontinued and quick medical help should be sought at the earliest sign of codeine toxicity including symptoms such as extreme sleepiness, confusion, or shallow breathing, which may be life threatening.

Patients with renal and hepatic impairment should consult a doctor before use.

A physician or pharmacist should be consulted before use if the patient is taking a serotonergic medicine.

Opioids have been associated with the following conditions:

- Adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure, which has been reported more often following greater than 1 month of use. Patients should seek medical attention if they experience a constellation of these symptoms.
- Androgen deficiency, which may present with non-specific symptoms and signs such as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. Patients should seek medical attention if they experience any of these symptoms.

- Serotonin syndrome, a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (see INTERACTIONS). Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare provider if they are taking, or plan to take serotonergic medications.

Pseudoephedrine

Tolerance with dependence may occur after continued use.

The effects of pseudoephedrine are lessened by medicines containing guanethidine, reserpine, methyldopa and may be diminished or enhanced by tricyclic antidepressants. It may increase the possibility of irregular heart beat in patients taking digitalis.

Patients with difficulty in urination due to enlargement of the prostate should be advised to consult a medical practitioner before using SINUMAX WITH CODEINE.

SINUMAX WITH CODEINE should be used under the direction of a medical practitioner in patients with pre-existing cardiovascular disease in particular those with coronary heart disease and hypertension.

Patients with thyroid disease or diabetes should not take pseudoephedrine unless directed by a medical practitioner.

Effects on Ability to Drive or Use Machines

Exercise caution when driving a motor vehicle or operating machinery.

INTERACTIONS

Alcohol and medicines that induce liver enzymes can increase the hepatotoxicity of paracetamol.

CNS depressants: Concomitant use with central nervous system depressants (e.g. barbiturates, chloral hydrate, benzodiazepines, phenothiazines, alcohol and centrally acting muscle relaxants) may cause additive CNS depression and respiratory depression.

Opioid analgesics: Concurrent use with other opioid receptor agonists may cause additive CNS depression, respiratory depression and hypotensive effects.

CYP2D6 inhibitors: Codeine analgesia is believed to be dependent upon the cytochrome P450 isoenzyme CYP2D6 catalysed o-demethylation to form the active metabolite morphine although other mechanisms have been cited. An interaction with quinidine, methadone, and paroxetine (CYP2D6 inhibitors) leading to decreased plasma concentrations of morphine has been described, which may have the potential to decrease codeine analgesia.

Serotonergic medicines: The concomitant use of opioids with other medicines that affect the serotonergic neurotransmitter system, such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, medicines that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and monoamine oxidase (MAO) inhibitors (used to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue), may result in serotonin syndrome.

Warfarin-like compounds: For most patients, occasional use of paracetamol generally has little or no effect on the International Normalised Ratio (INR) in patients on chronic warfarin therapy;

however, there has been controversy regarding the possibility of paracetamol potentiating the anticoagulant effects of warfarin and other coumarin derivatives. Patients should be instructed to ask a doctor or pharmacist before use if they are taking blood thinning medicine warfarin or other coumarin derivatives.

Monoamine Oxidase Inhibitors (MAOIS): Pseudoephedrine exerts its vasoconstricting properties by stimulating adrenergic receptors and displacing norepinephrine from neuronal storage sites. Since MAOIs impede the metabolism of sympathomimetic amines and increase the store of releasable norepinephrine in adrenergic nervous tissue, MAOIs may potentiate the pressor effect of pseudoephedrine. Acute hypertensive crises have been reported in the medical literature with the concomitant use of MAOIs and sympathomimetic amines.

HUMAN REPRODUCTION

Do not take this product during pregnancy or whilst breastfeeding.

There are no adequate and well-controlled clinical studies of the combination of paracetamol and codeine in pregnant or breastfeeding women.

The combination of codeine and paracetamol is contraindicated in breastfeeding women.

Codeine - Pregnancy

Codeine crosses the placenta. Neonates who have been exposed to codeine in utero can develop withdrawal syndrome (neonatal abstinence syndrome) after delivery. Cerebral infarction has been reported in this setting.

Paracetamol – Pregnancy

When given to the mother in labelled doses, paracetamol crosses the placenta into foetal circulation as early as 30 minutes after ingestion and is effectively metabolised by foetal sulfate conjugation. When taken as directed, paracetamol does not adversely affect the pregnant mother or foetus.

Codeine - Lactation

Codeine and its active metabolite, morphine, are secreted into human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose dependent.

Despite the common use of codeine medicines to manage postpartum pain, reports of adverse events in infants are rare. However, some women rapidly metabolise codeine, which may result in higher serum levels of codeine's active metabolite, morphine, in breast milk and, therefore, potentially dangerously high levels of serum morphine in their breastfed infants. Deaths have occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolisers of codeine. Maternal use of codeine can lead to potentially serious adverse reactions, including death, in nursing infants.

Codeine is contraindicated in breastfeeding women.

Paracetamol - Lactation

Paracetamol is excreted in breast milk in low concentrations (0,1 % to 1,85 % of the ingested maternal dose). Maternal ingestion of paracetamol in labeled doses does not present a risk to the nursing infant.

Pseudoephedrine - Lactation

Pseudoephedrine distributes into and is concentrated in breast milk. Up to 0,7 % of a single 60 mg dose of pseudoephedrine may be distributed into breast milk over 24 hours. Pseudoephedrine concentrations in milk are from 2 to 3 fold higher than those in plasma. This milk/plasma medicine concentration profile suggests low protein binding, although no protein plasma binding data in humans are available. Data from a study of lactating mothers taking 60 mg pseudoephedrine every 6 hours suggests that from 2,2 to 6,7 % of the maximum daily dose (240 mg) may be available to the infant from a breastfeeding mother.

DOSAGE AND DIRECTIONS FOR USE

DO NOT EXCEED THE RECOMMENDED DOSE.

Adults and children over 12 years: ONE to TWO tablets every four to six hours. Do not exceed eight tablets in 24 hours.

Children and Adolescents aged 12 to 18 years:
Use only under the supervision of a healthcare professional.

Do not use for longer than 5 days. SINUMAX WITH CODEINE should be taken at the lowest effective dose for the shortest period of time.

Not recommended for children under 12 years.

SIDE EFFECTS

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

System organ class	Adverse event
Infections and infestations	Pharyngitis
Immune system disorders	Allergic reactions, anaphylactic reaction, hypersensitivity.
Skin and subcutaneous tissue disorders	Urticaria, dermatitis, skin rash and other allergic reactions. The rash is usually erythematous or urticarial and may be accompanied by fever and mucosal lesions. Pruritus/itching, sweating, facial flushing, angioedema, rash pruritic, fixed eruption.
Blood and lymphatic system disorders	Leukopaenia, pancytopaenia, neutropaenia, haemolysis (in patients with glucose-6-phosphate dehydrogenase).
Nervous system disorders	Headache, dizziness, psychomotor hyperactivity, sedation, somnolence, tremor, restlessness.
Gastro-intestinal disorders	Nausea, vomiting, constipation, dry mouth, thirst, abdominal pain, dyspepsia, diarrhoea.
Psychiatric disorders	Insomnia, anxiety, agitation, dependence, drug withdrawal syndrome, euphoric mood, hallucination, restlessness,

	somnolence/sleepiness, confusion, mood changes.
Cardiac disorders	Tachycardia, ventricular dysrhythmia, precordial pain, palpitations, bradycardia, hypertension.
Musculoskeletal and connective tissue disorders	Muscular weakness.
Renal and urinary disorders	Difficulty in urination with kidney duct or bile duct spasm, dysuria, urinary retention.
Eye disorders	Contraction of the pupil of the eye.
Respiratory, thoracic and mediastinal disorders	Bronchospasm, dyspnoea, respiratory depression.
Vascular disorders	Postural hypotension, increased pressure inside the skull, flushing.
General disorders	Fever, abnormally low body temperature, irritability.
Investigations	Increased blood pressure, increased transaminases*
*Low level transaminase elevations may occur in some patients taking labelled doses of paracetamol; these elevations are not accompanied with liver failure and usually resolve with continued therapy or discontinuation of paracetamol.	

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

If more than the recommended dose has been taken speak to your doctor or take the patient to the nearest hospital immediately.

For additional emergency information, call your nearest poison centre.

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 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 arrhythmias have been reported.

Hepatobiliary Disorders

If a paracetamol extended release product is involved or if the exact formulation is not known, it is recommended to obtain an additional plasma paracetamol level 4 to 6 hours following the initial paracetamol level as these levels will continue to rise with the extended release products and may alter treatment decisions.

In adults and adolescents (≥ 12 years of age), hepatic toxicity may occur following ingestion of greater than 7,5 to 10 grams over a period of 8 hours or less.

Fatalities are infrequent (less than 3-4 % of untreated cases) and have rarely been reported with overdoses of less than 15 grams. In children (< 12 years of age), an acute overdosage of less than 150 mg/kg has not been associated with hepatic toxicity.

Early symptoms following a potentially hepatotoxic overdose may include: anorexia, nausea, vomiting, diaphoresis, pallor and general malaise.

Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Serious toxicity or fatalities have been extremely infrequent following an acute paracetamol overdose in young children, possibly because of differences in the way they metabolise paracetamol.

The following are clinical events associated with paracetamol overdose that if seen with overdose are considered expected, including fatal events due to fulminant hepatic failure or its sequelae.

Adverse Reactions Identified with Overdose of Paracetamol	
System Organ Class	**Preferred Term**
Metabolism and Nutrition Disorders	Decreased appetite
Gastrointestinal Disorders	Abdominal discomfort
	Nausea
	Vomiting
Hepatobiliary Disorders	Acute hepatic failure
	Hepatic necrosis
	Hepatomegaly
	Jaundice
	Liver tenderness
General Disorders and Administration Site Conditions	Hyperhidrosis
	Malaise
	Pallor
Investigations	Increased blood bilirubin
	Increased blood lactic acid
	Increased blood phosphorus
	Increased hepatic enzymes
	Increased international normalised ratio
	Prolonged prothrombin time prolonged

The following clinical events are sequelae to acute hepatic failure and may be fatal. If these events occur in the setting of acute hepatic failure associated with paracetamol overdose (adults and adolescents: ≥ 12 years of age: > 7,5 mg within 8 hours; children < 12 years of age: >150 mg/kg within 8 hours), they are considered expected.

Expected sequelae to acute hepatic failure associated with paracetamol overdose include the following: Bacterial infection, fungal infection, sepsis, coagulopathy, disseminated intravascular coagulation, thrombocytopenia, hypoglycaemia, hypophosphataemia, lactic acidosis, metabolic acidosis, brain oedema, coma (with massive paracetamol overdose or multiple drug overdose), encephalopathy, cardiomyopathy, hypotension, respiratory failure, gastrointestinal haemorrhage, pancreatitis, acute kidney injury, and multiple organ dysfunction syndrome.

Blood and Lymphatic Disorders

Haemolytic anaemia (in patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency): Haemolysis has been reported in patients with G6PD deficiency, with use of paracetamol in overdose.

In the event of overdose, get medical help or contact a Poison Control Center right away.

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.

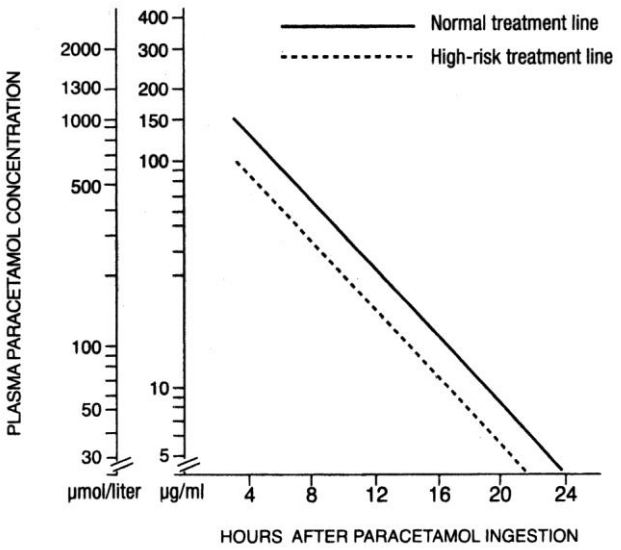
Ingestion of amounts of paracetamol smaller than this may require treatment in patients susceptible to paracetamol poisoning (see above). In patients who are stuperose or comatose endotracheal intubation should precede gastric lavage in order to avoid aspiration.

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. 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 normogram below.



Source: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th Ed.

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.

Pseudoephedrine

Symptoms from pseudoephedrine overdose consist most often of mild anxiety, increased rate of heart beat and/or mild high blood pressure. Symptoms usually appear within 4 to 8 hours of being taken.

Overdosage may result in nausea, vomiting, sympathomimetic symptoms, including central nervous system stimulation, insomnia, tremor, mydriasis, anxiety, agitation, hallucinations, seizures, palpitations, tachycardia, hypertension, and reflex bradycardia. Other effects may include dysrhythmias, hypertensive crisis, intracerebral haemorrhage, myocardial infarction, psychoses, rhabdomyolysis, hypokalaemia, and ischemic bowel infarction. Drowsiness has been reported with overdose in children.

Codeine

Risks of codeine overdose include cardio-respiratory arrest, brain oedema, coma, confusional state, seizure, hypotension, hypoxia, ileus, miosis, renal failure, respiratory depression and respiratory failure, stupor and vomiting,

Agitation and/or seizure in particular can occur in young children following overdose.

The specific antagonist, naloxone hydrochloride may be used to counteract severe respiratory depression.

IDENTIFICATION

A flat round, white tablet with bevelled edges and "SINUMAX CO" embossed on the one side and a breakline on the other side.

PRESENTATION

Securitainers of 20 tablets.

STORAGE INSTRUCTIONS

Store at or below 25 °C. Protect from light, moisture and exposure to air.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER

29/5.8/0004

Namibia Reg. Nr.:
Sinumax with Codeine: 04/5.8/0295
NS 2

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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