Professional information for SINUTAB® SINUS PAIN NON-DROWSY

SCHEDULING STATUS:

S2

1. NAME OF THE MEDICINE

SINUTAB® SINUS PAIN NON-DROWSY tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Pseudoephedrine hydrochloride	30 mg
Paracetamol	500 mg

Sugar free.

3. PHARMACEUTICAL FORM

Tablets.

A white, round, biconvex tablet, with a score on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of symptoms of nasal, sinus and Eustachian tube mucosal congestion and associated pain and fever due to colds and influenza.

4.2 Posology and method of administration

Adults and children over 12 years:

Two tablets every four to six hours.

Do not exceed eight tablets in 24 hours.

Not be used in children below the age of 12 years.

The Elderly:

There have been no specific studies of SINUTAB® SINUS PAIN NON-DROWSY in the elderly.

Experience has indicated that normal adult dosage is appropriate.

In the elderly the rate and extent of paracetamol absorption is normal but plasma half life is longer and paracetamol clearance is lower than in young adults.

Hepatic dysfunction:

Caution should be exercised when administering SINUTAB® SINUS PAIN NON-DROWSY to patients with severe hepatic impairment.

Renal dysfunction:

Caution should be exercised when administering SINUTAB® SINUS PAIN NON-DROWSY to patients with moderate to severe renal impairment.

Method of administration

For oral use.

DO NOT EXCEED THE RECOMMENDED DOSE.

4.3 Contraindications

- Hypersensitivity to paracetamol, pseudoephedrine, or to any of the ingredients (see section 4.8).
- SINUTAB® SINUS PAIN NON-DROWSY is contraindicated in persons receiving monoamine

oxidase inhibitor (MAOI) treatment or within 14 days of ceasing such treatment.

- Contraindicated in most forms of cardiovascular disease, including angina and hypertension, and also in hyperthyroidism, phaeochromocytoma and closed angle glaucoma.
- Severe liver disease.
- Should be avoided in patients undergoing inhalation anaesthesia.

4.4 Special warnings and precautions for use

SINUTAB® SINUS PAIN NON-DROWSY 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 continuously for more than ten days; if symptoms persist, irrespective of therapy used, consult your doctor. Dosages in excess of those recommended may provoke severe liver, kidney, and cardiovascular repercussions.

Do not use this product without consulting a doctor or pharmacist if you are presently taking monoamine oxidase inhibitors or other medicines for depression, psychiatric or emotional conditions or hypertension or other cardiovascular conditions (see section 4.3).
Do not take concurrently with any other paracetamol- or sympathomimetic-containing medicines.

Chronic alcohol users should ask their physician whether they should take paracetamol or other pain relievers or fever reducers.

Patients with impaired kidney or liver function should take paracetamol under medical supervision

only.

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 SINUTAB® SINUS PAIN NON-DROWSY should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

SINUTAB® SINUS PAIN NON-DROWSY should not be used by patients with cardiovascular disease, hyperthyroidism, liver disease, renal disease, difficulty in urination and/or enlargement of the prostate, glaucoma or diabetes (see section 4.3).

There have been reports of ischaemic colitis with pseudoephedrine. SINUTAB® SINUS PAIN NON-DROWSY should be discontinued and medical advice sought if sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis develop (see section 4.8).

Severe skin reactions such as acute generalised exanthematous pustulosis (AGEP) have been reported with pseudoephedrine-containing medicines, such as SINUTAB® SINUS PAIN NON-DROWSY. This acute pustular eruption may occur within the first 2 days of treatment, with fever, and numerous, small, mostly non-follicular pustules arising on a widespread oedematous erythema and mainly localised on the skin folds, body, and upper extremities. Patients should be carefully monitored. If signs and symptoms such as formation of small pustules occur, with or without pyrexia or erythema, then treatment with pseudoephedrine should be discontinued and a doctor should be consulted.

If symptoms persist or get worse, or if new symptoms occur, patients should stop use and consult a doctor.

4.5 Interaction with other medicines and other forms of interaction

Combinations containing any of the following medicines, depending on the amount present, may also interact with SINUTAB® SINUS PAIN NON-DROWSY.

Cardiac arrythmias may occur when pseudoephedrine is used prior to anaesthesia with inhalation anaesthetics such as chloroform, cyclopropane, enflurane, halothane, isoflurane, methoxyflurane, and trichloroethylene or concurrently with digitalis glycosides.
Concurrent use of tricyclic antidepressants with SINUTAB® SINUS PAIN NON-DROWSY may potentiate the cardiovascular effects of sympathomimetic amines.
When diuretics or antihypertensives are used concurrently with sympathomimetic amines the antihypertensive effects may be reduced.

Concurrent use of beta-adrenergic blocking agents with sympathomimetic amines may result in significant hypertension and excessive bradycardia with possible heart block.
CNS stimulants used concurrently with pseudoephedrine may result in additive CNS stimulation to excessive levels, which may cause unwanted effects, such as nervousness, irritability, insomnia, or possibly convulsions or cardiac arrythmias.
Doxapram used concurrently with SINUTAB® SINUS PAIN NON-DROWSY may increase the pressor effects of either doxapram or sympathomimetic amines.

Monoamine oxidase (MAO) inhibitors used concurrently with sympathomimetic amines may

prolong and intensify the cardiac stimulant and vasopressor effects of pseudoephedrine. These medicines should not be administered during or within 14 days following the administration of a MAO inhibitor (see section 4.3).

Concurrent use with rauwolfia alkaloids may inhibit the indirect-acting sympathomimetic action of pseudoephedrine.

The risk of hepatotoxicity with single toxic doses or prolonged use of high doses of paracetamol may be increased in alcoholics or in patients regularly taking other hepatoxic medicines or hepatic enzyme inducers.
Prolonged concurrent use of paracetamol with other NSAIDs may also increase the risk of adverse renal effects.

Paracetamol may competitively inhibit the hepatic glucuronidation and decrease the clearance of zidovudine; zidovudine may also inhibit the hepatic glucuronidation of paracetamol.
Aluminium hydroxide containing preparations may increase the absorption rate of pseudoephedrine hydrochloride.

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 consult a doctor or pharmacist before use if they are taking warfarin or other coumarin derivatives.

4.6 Fertility, pregnancy and lactation

There are no adequate and well-controlled clinical studies in pregnant or breast-feeding women for the combination of paracetamol and pseudoephedrine.

This product should not be used during pregnancy or lactation.

Pregnancy

The safety of pseudoephedrine in pregnancy has not been established.

Breastfeeding

Pseudoephedrine is excreted in breast milk in small amounts. Paracetamol is excreted in breast milk but not in a clinically significant amount.

Fertility

No studies have been conducted in animals to determine whether pseudoephedrine has the potential to impair fertility. There is no information of the effect of SINUTAB® SINUS PAIN NON-DROWSY on fertility.

4.7 Effects on ability to drive and use machines

It is not known if SINUTAB® SINUS PAIN NON-DROWSY has an effect on the ability to drive or operate machinery. As dizziness can occur patients are advised not to drive or operate machinery until they know how SINUTAB® SINUS PAIN NON-DROWSY affects them.

4.8 Undesirable effects

Paracetamol:

Blood and lymphatic system disorders

Less frequent: neutropenia, pancytopenia, leucopenia, thrombocytopenia

Immune system disorders

Less frequent: sensitivity/allergic reactions resulting in skin rash, laryngeal oedema, angioedema and anaphylaxis

Skin and subcutaneous tissue disorders

Less frequent: erythematous rash, urticarial rash

Gastrointestinal disorders

Less frequent: mucosal lesions, pancreatitis

General disorders and administration site conditions

Less frequent: fever

Pseudoephedrine hydrochloride:

Metabolism and nutrition disorders

Less frequent: decreased appetite, hypokalaemia, altered metabolism

Psychiatric disorders

Frequent: fear, anxiety, insomnia, confusion, irritability, psychotic states

Nervous system disorders

Frequent: restlessness, tremor, dizziness

Less frequent: cerebral haemorrhage, headache

Cardiac disorders

Less frequent: pulmonary oedema, cardiac dysrhythmias, anginal pain, palpitations, and cardiac arrest

Vascular disorders

Less frequent: hypertension, reflex bradycardia, tachycardia, hypotension, flushing, fainting

Respiratory, thoracic and mediastinal disorders

Less frequent: dyspnoea

Gastrointestinal disorders

Less frequent: nausea, vomiting, hypersalivation

Renal and urinary disorders

Less frequent: difficulty in micturition, urinary retention.

General disorders and administration site conditions

Frequent: weakness, sweating, tolerance with dependence

Investigations

Less frequent: changes in blood sugar levels

Pseudoephedrine/Paracetamol combination

Psychiatric disorders:

*Frequent: n*ervousness

Post-marketing experience:

The following adverse drug reactions were identified during post-marketing experience with paracetamol, pseudoephedrine by frequency category estimated from clinical trials or epidemiology studies:

Immune system disorders:

Frequency unknown: Anaphylactic reaction, hypersensitivity.

Psychiatric disorders:

Frequency unknown: Anxiety, euphoric mood, hallucination, visual hallucination, restlessness.

Nervous system disorders:

Frequency unknown: Cerebrovascular accident, headache, paraesthesia, psychomotor hyperactivity, tremor.

Cardiac disorders:

Frequency unknown: Dysrhythmia, myocardial infarction, palpitations, tachycardia.

Gastrointestinal disorders:

Frequency unknown: Abdominal pain, colitis ischaemic, diarrhoea, vomiting.

Skin and subcutaneous tissue disorders:

Frequency unknown: Acute generalised exanthematous pustulosis, angioedema, fixed eruption, pruritus, rash, pruritic rash, urticaria.

Renal and urinary disorders:

Frequency unknown: Dysuria, urinary retention.

Investigations:

Frequency unknown: Increased blood pressure, increased transaminases.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of SINUTAB® SINUS PAIN NON-DROWSY TABLETS is important. It allows continued monitoring of the benefit/risk balance of SINUTAB® SINUS PAIN NON-DROWSY TABLETS. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

See sections 4.4 and 4.8.

Paracetamol:

Nausea, vomiting and anorexia. Liver damage, which may be fatal, may only appear after a few days. Acute intoxication may cause kidney failure.

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 arrhythmias 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 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.

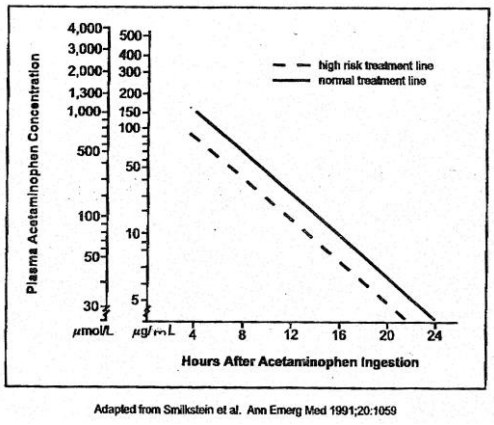
An initial dose of 150 mg/kg N-acetylcysteine in 200 ml dextrose injection given intravenously over 15 minutes, followed by an infusion of 50 mg/kg in 500 ml dextrose injection over the next four hours, and then 100 mg/kg in 1000 ml dextrose injection over the next sixteen hours. The volume of intravenous 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 nomogram below



Adapted from Smilkstein et al. Ann Emerg Med 1991;20:1059

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 hydrochloride:

Convulsions and hyperpyrexia in children due to cerebral stimulation. In adults, symptoms of stimulation include insomnia, nervousness, tachycardia, tremors, muscle twitching and convulsions. Severe cardiovascular repercussions include hypertension, angina, arrhythmias, myocardial infarction and cerebral haemorrhage.

Treatment of overdose:

To decrease absorption:

Because pseudoephedrine is rapidly absorbed from the gut, emetics and gastric lavage should be instituted within 4 hours of overdosage in order to be effective. Charcoal is useful only if administered within 1 hour.

To enhance elimination:

Forced diuresis will increase elimination of pseudoephedrine provided renal function is adequate; however, diuresis is not recommended for severe overdosage.

Specific treatment:

For delirium or convulsions, intravenous diazepam may be administered.

The cardiac state should be monitored and serum electrolytes measured. If there are signs of cardiac toxicity, intravenous propranolol may be indicated.

Hypokalaemia may be treated, if necessary, with a slow infusion of a dilute potassium chloride solution; serum potassium concentration should be monitored during and for several hours after administration of potassium chloride.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Pharmacotherapeutic group: Other analgesics and antipyretics: paracetamol, combinations excl. psycholeptics

ATC code: N02BE51

SINUTAB® SINUS PAIN NON-DROWSY has analgesic, anti-pyretic and sympathomimetic properties.

5.2 Pharmacokinetic properties

Absorption:

Paracetamol

Oral paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract, primarily in the small intestine. Absorption occurs by passive transport. The rate of oral absorption depends mainly upon the rate of gastric emptying. The relative bioavailability ranges from 85 % to 99 %. Peak plasma concentrations are usually attained about 30 – 60 minutes after oral dosing. For individual adults, maximum plasma concentrations occur within 1 hour following ingestion, and range from 14,8 to 17,6 µg/mL for a single 1 000 mg dose. Maximum plasma concentrations at steady state after 1 000 mg doses every 6 hours range from 17,6 to 18,2 µg/mL.

Pseudoephedrine

Pseudoephedrine is rapidly absorbed from the gastrointestinal tract. The oral bioavailability of pseudoephedrine is high, as determined by urine collections greater than 96 % of administered doses. When pseudoephedrine is taken after a high-fat meal, the absorption rate is decreased, resulting in about an hour delay in attaining maximum concentrations.

Following oral administration of a single 30 mg tablet, a mean maximum plasma concentration of 104 ± 19 ng/mL is attained in 1,46 ± 0,55 hours. Following oral administration of a single 60 mg dose as tablets, mean maximum plasma concentrations of 180 ± 30 and 232 ± 30 ng/mL are attained at 1,94 ± 0,86 and 1,96 ± 0,62 hours, respectively.

Distribution:

Paracetamol

Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is 0,7 to 1 L/kg in children and adults. A relatively small proportion

(10 % to 25 %) of paracetamol is bound to plasma protein.

Pseudoephedrine

The apparent volume of distribution for pseudoephedrine ranges from 2,3 to 3,3 L/kg. 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 drug 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.

Biotransformation:

Paracetamol

Paracetamol is primarily metabolised in the liver and involves three main pathways: conjugation with glucuronide; conjugation with sulphate; and oxidation via cytochrome P450 enzyme pathway. The oxidative pathway forms a reactive intermediate, which is detoxified by conjugation with glutathione to form inert cysteine and mercapturic acid metabolites. The principal cytochrome P450 isoenzyme involved *in vivo* appears to be CYP2E1, although CYP1A2 and CYP3A4 were considered minor pathways based on *in vitro* microsomal data. Subsequently, both CYP1A2 and CYP3A4 were found to have negligible contribution *in vivo*.

Pseudoephedrine

In adults, only a minor fraction of pseudoephedrine is metabolised in the liver. About 1 % to 6,2 % of a dose undergoes N-demethylation to the metabolite, norpseudoephedrine, which is excreted in the urine.

Elimination:

Paracetamol

The elimination half-life of paracetamol is about 1 to 3,5 hours. It is approximately one hour longer in neonates and in cirrhotic patients. Paracetamol is eliminated from the body as glucuronide (45 – 60 %) and sulphate (25 – 35 %) conjugates, thiols (5 – 10 %) as cysteine and mercapturate metabolites, and catechols (3 – 6 %) that are excreted in the urine. Renal clearance of unchanged paracetamol is about 3,5 % of the dose.

Pseudoephedrine

Pseudoephedrine is mainly eliminated by renal excretion as unchanged medicine. Most of an oral dose (43 % to 96 %) is excreted unchanged in the urine within 24 hours. In adults, the elimination half-life (t½) for both immediate- and extended-release pseudoephedrine ranges from 5,5 to 7,0 hours. Oral clearance of pseudoephedrine is approximately 7,3 to 7,6 mL/min/kg.
Urinary pH affects the elimination t½ and clearance of pseudoephedrine due to extensive reabsorption in the renal tubules at alkaline pH; renal reabsorption is negligible at acidic pH. In a study in which participants received sodium bicarbonate to adjust their urine to an alkaline range and ammonium chloride tablets to adjust their urine to an acidic range, an alkaline urinary pH of 8,0 prolonged the t½ (range, 9,2 to 16,0 hours) and an acidic urinary pH of 5,0 reduced the t½ of pseudoephedrine (range, 3,0 to 6,4 hours). In a study which monitored but did not adjust urinary pH, the t½ of pseudoephedrine in urine ranged from 1,9 hours at pH 5,66 to 21 hours at pH 7,80.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone

Magnesium stearate

Microcrystalline cellulose

Povidone

Pregelatinised maize starch

Sodium starch glycollate

Stearic acid.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a cool place, at or below 25 ºC.

Protect from light and moisture.

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

6.5 Nature and contents of container

Cartons containing white opaque or clear blisters in packs of 10 and 20 tablets.

6.6 Special precautions for disposal and other handling

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Johnson & Johnson (Pty) Ltd.

241 Main Road

Retreat

7945

SOUTH AFRICA

8. REGISTRATION NUMBER

37/5.8/0138

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 April 2009

10. DATE OF REVISION OF THE TEXT

20 April 2022

EXPORT REGISTRATION DETAILS

Namibia NS1 15/5.8/0177

Zimbabwe: 2016/22.2.5/5246 P