Professional information for SUDAFED® SINUS PAIN

SCHEDULING STATUS:

S2

1. NAME OF THE MEDICINE

SUDAFED® SINUS PAIN tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Pseudoephedrine hydrochloride	60 mg
Paracetamol	500 mg

Sugar free.

3. PHARMACEUTICAL FORM

Tablets.

A white, elongated tablet with flat-bevelled edges, having a score on the one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SUDAFED® SINUS PAIN is indicated for the symptomatic relief of nasal, sinus and Eustachian tube mucosal congestion associated with pain and pyrexia due to the common cold and influenza.

4.2 Posology and method of administration

Adults and children over 12 years: One tablet orally three times daily.

Children under 12 years: Not recommended.

Do not exceed the stated dose, if symptoms persist, consult a doctor.

Hepatic impairment

Caution should be exercised when administering SUDAFED® SINUS PAIN to patients with severe hepatic impairment.

Renal impairment

Caution should be exercised when administering SUDAFED® SINUS PAIN 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 pseudoephedrine, paracetamol or to any of the ingredients (see section 6.1).
- SUDAFED® SINUS PAIN is contraindicated in patients who are taking or have taken monoamine oxidase inhibitors within the preceding two weeks as this may cause a rise in blood pressure. The antibacterial agent furazolidone is known to cause a dose-related inhibition of monoamine oxidase. SUDAFED® SINUS PAIN and furazolidone should not be taken together.
- Due to its paracetamol content, SUDAFED® SINUS PAIN should not be used in cases of severe liver impairment.
- The safety of SUDAFED® SINUS PAIN in pregnancy has not been established.
- Diabetes mellitus.
- Patients undergoing inhalation anaesthesia.
- Phaeochromocytoma.

- Hyperthyroidism.
- Severe renal impairment.
- Closed-angle glaucoma.
- Difficulty in urination and/or enlargement of the prostate.
- Cardiovascular disease including hypertension.
- Do not take concurrently with any other paracetamol-or sympathomimetic-containing medicines.

4.4 Special warnings and precautions for use

SUDAFED® SINUS PAIN 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 of SUDAFED® SINUS PAIN in excess of those recommended, may cause severe liver damage.

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

Consult your doctor if no relief is obtained from the recommended dosage. Do not use continuously for more than 10 days without consulting a doctor.

Do not use SUDAFED® SINUS PAIN with any other product containing paracetamol (see section 4.3).

Alcohol may increase the hepatotoxicity of paracetamol and may contribute to acute pancreatitis. Chronic alcohol users should ask their doctor whether they should take paracetamol or other pain relievers or fever reducers.

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 SUDAFED® SINUS PAIN must immediately be discontinued and appropriate treatment instituted.

Patients should be informed about the signs of serious skin reactions and use of SUDAFED® SINUS PAIN should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

SUDAFED® SINUS PAIN should not be used by patients with cardiovascular disease such as coronary heart disease, arrhythmia or tachycardia, occlusive vascular disorders including arteriosclerosis, hypertension or aneurysms. Pseudoephedrine, as contained in SUDAFED® SINUS PAIN, should not be given to patients with, hyperthyroidism, diabetes, closed-angle glaucoma, decreased kidney function, difficulty in urination and/or enlargement of the prostate. There have been reports of ischaemic colitis with pseudoephedrine. SUDAFED® SINUS PAIN 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 SUDAFED® SINUS PAIN. 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 SUDAFED® SINUS PAIN 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.

Caution is advised if paracetamol, as contained in SUDAFED® SINUS PAIN, is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended (see section 4.5).

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors (MAOIs)

Pseudoephedrine exerts its vasoconstricting properties by stimulating α- adrenergic receptors and displacing noradrenaline from neuronal storage sites. Since MAOIs impede the metabolism of sympathomimetic amines and increase the store of releasable noradrenaline in adrenergic nerve endings, MAOIs may potentiate the pressor effect of pseudoephedrine. SUDAFED® SINUS PAIN should not be used in patients taking monoamine inhibitors or within 14 days of stopping treatment as there is a risk of hypertensive crisis (see section 4.3).

Moclobemide

Risk of hypertensive crisis.

Sympathomimetic medicines

Concomitant use of SUDAFED® SINUS PAIN with sympathomimetic medicines such as decongestants, tricyclic antidepressants, appetite suppressants and amphetamine-like psychostimulants, antihypertensive medicines or with monoamine oxidase inhibitors, which interfere with the catabolism of sympathomimetic amines, may cause a rise in blood pressure.

Pseudoephedrine may partially reverse the hypotensive action of medicines, which interfere with sympathetic activity including bretylium, bethanidine, guanethidine, debrisoquine and methyldopa.

Pseudoephedrine as contained in SUDAFED® SINUS PAIN should not be used in patients undergoing anaesthesia with cyclopropane, halothane or other halogenated anaesthetics as they may induce ventricular fibrillation (see section 4.3). An increased risk of arrhythmias may also occur if pseudoephedrine is given to patients receiving cardiac glycosides, quinidine or tricyclic antidepressants. Chronic ingestion of anticonvulsants and oral steroid contraceptives induces liver enzymes and may prevent attainment of therapeutic paracetamol levels by increasing first pass metabolism and clearance.

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.

Flucloxacillin

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risks factors (see section 4.4).

Concomitant use of SUDAFED® SINUS PAIN with hepatotoxic medicines or medicines that induce liver enzymes may increase the risk of toxicity of SUDAFED® SINUS PAIN.

Metoclopramide and domperidone may accelerate the absorption of paracetamol.

Probenecid may decrease the clearance and increase the plasma half-life of paracetamol.

Colestyramine reduces the absorption of paracetamol if given within one hour of SUDAFED®

SINUS PAIN.

Prolonged concurrent use of SUDAFED® SINUS PAIN with salicylates increases the risk of adverse renal effects.

4.6 Fertility, pregnancy and lactation

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

SUDAFED® SINUS PAIN is not recommended during pregnancy or lactation.

Pregnancy

The safety of pseudoephedrine in pregnancy has not been established.

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Breastfeeding

Pseudoephedrine is excreted in breast milk in small amounts but the effect of this on breastfed infants is not known. It has been estimated that approximately 0,4 to 0,7 % of a single 60 mg dose of pseudoephedrine ingested by a nursing mother will be excreted in the breast milk over 24 hours. 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.

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breastfeeding. A pharmacokinetic study of paracetamol in 12 nursing mothers revealed that less than 1 % of a 650 mg oral dose of paracetamol appeared in the breast milk. Similar findings have been reported in other studies, therefore maternal ingestion of therapeutic doses of paracetamol does not appear to present a risk to the infant.

Fertility

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

4.7 Effects on ability to drive and use machines

It is not known if SUDAFED® SINUS PAIN 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 SUDAFED® SINUS PAIN affects them.

4.8 Undesirable effects

Pseudoephedrine/Paracetamol combination

Blood and the lymphatic system disorders:

Less frequent: Neutropenia, pancytopenia, leukopenia, thrombocytopenic purpura, haemolytic anaemia, agranulocytosis.

Psychiatric disorders:

Frequent: Nervousness.

Less frequent: Insomnia, confusion, irritability, psychotic states, hallucinations, fear, anxiety, restlessness.

Nervous system disorders:

Frequent: Headache.

Less frequent: Tremor.

Skin and subcutaneous tissue disorders:

Less frequent: Fixed drug eruption.

Renal and urinary disorders:

Less frequent: Papillary necrosis, urinary retention.

General disorders:

Less frequent: Weakness.

Post-marketing experience:

The following adverse 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, allergic reactions.

Metabolism and nutrition disorders:

Frequency unknown: Reduced appetite, disturbances of glucose metabolism.

Psychiatric disorders:

Frequency unknown: Euphoric mood, sleep disturbance.

Nervous system disorders:

Frequency unknown: Cerebrovascular accident, paraesthesia, psychomotor hyperactivity, posterior reversible encephalopathy syndrome (PRES), reversible cerebral vasoconstriction syndrome (RCVS).

Cardiac disorders:

Frequency unknown: Arrhythmia, myocardial infarction, palpitations, tachycardia, cardiac arrhythmias, angina (in patients with angina pectoris), anginal pain, cardiac arrest, hypotension with dizziness, fainting and flushing.

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: Dyspnoea.

Gastrointestinal disorders:

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

Skin and subcutaneous tissue 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), angioedema, pruritus, rash, pruritic rash, urticaria, sweating.

Renal and urinary disorders:

Frequency unknown: Dysuria.

Investigations:

Frequency unknown: Increased blood pressure (possibly resulting in cerebral haemorrhage or pulmonary oedema), increased transaminases.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of SUDAFED® SINUS PAIN is important. It allows continued monitoring of the benefit/risk balance of SUDAFED® SINUS PAIN. Health care 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.

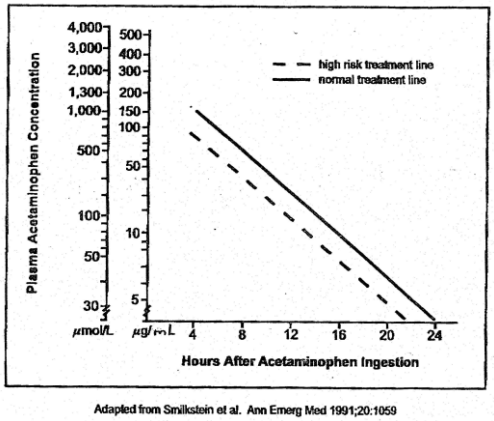
***N*-acetylcysteine** should be administered to all cases of suspected overdose as soon as possible, preferably within eight hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken.

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

Those whose 

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

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

The effect of acute toxicity from overdosage with pseudoephedrine may include irritability, convulsions, hypertension, restlessness, tremor and difficulty with micturition. Necessary measures should be taken to maintain and support respiration and circulation. Gastric lavage should be performed if indicated. Specialised treatment is essential as soon as possible.

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

SUDAFED® SINUS PAIN has decongestive, analgesic and antipyretic actions.

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

Magnesium stearate

Microcrystalline cellulose

Povidone

Sodium starch glycollate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light and moisture.

6.5 Nature and contents of container

PVC/PVDC / aluminium blister packs of 10 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

T/5.8/196

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 June 1992

10. DATE OF REVISION OF THE TEXT

20 February 2024

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EXPORT REGISTRATION DETAILS

Botswana: B9317145