

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Non-drowsy Sinutab Tablets
Paracetamol 500mg
Pseudoephedrine hydrochloride 30mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30 mg Pseudoephedrine hydrochloride and 500 mg Paracetamol.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White round biconvex tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Non-drowsy Sinutab is indicated for the short term symptomatic relief of conditions where congestion of the mucous membranes of the upper respiratory tract, especially nasal mucosa and sinuses, is accompanied by mild to moderate pain or pyrexia, eg the common cold, influenza, sinusitis and nasopharyngitis.

4.2 Posology and method of administration

Posology:

Adults and Children aged 12 years and over

Two tablets to be taken every four to six hours, up to four times a day.
Maximum daily dose: 8 tablets (240 mg pseudoephedrine and 4 g paracetamol).

Children under 12 years:

This medicine is contraindicated in children under the age of 12 years (see section 4.3).

Use in the Elderly

There have been no specific studies of this medicine in the elderly. Experience has indicated that normal adult dosage is appropriate.

Hepatic dysfunction:

Caution should be exercised when administering the product to patients with severe hepatic impairment.

Renal dysfunction:

Caution should be exercised when administering Non-drowsy Sinutab to patients with mild to moderate renal impairment.

Duration of use:

Patients should be advised not to use this product for more than 5 days and to seek medical advice if symptoms persist.

Do not exceed the stated dose.

Keep out of the sight and reach of children.

Method of administration:

For oral use.

4.3 Contraindications

Hypersensitivity to paracetamol, pseudoephedrine or to any of the excipients listed in section 6.1

This product is contra-indicated in patients with:

- Cardiovascular disease including hypertension
- Diabetes mellitus
- Pheochromocytoma
- Hyperthyroidism
- Closed angle glaucoma
- Severe renal impairment

This product should not be used concomitantly with (see section 4.5):

- Monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs. The concomitant use of pseudoephedrine and these products may cause a rise in blood pressure or hypertensive crisis.
- Other sympathomimetic decongestants
- Furazolidone
- Beta-blockers. This medicine is contraindicated in patients at risk of developing respiratory failure.

Not to be used in children under 12 years of age.

4.4 Special warnings and precautions for use

Use with caution in patients with hepatic impairment, mild to moderate renal impairment or difficulty in urination due to prostatic enlargement.

The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

Although pseudoephedrine has virtually no pressor effects in normotensive patients, this medicine should be used with caution in patients taking other sympathomimetic agents (such as appetite suppressants and amphetamine-like psychostimulants). The physician or pharmacist should check that sympathomimetic containing preparations are not simultaneously administered by several routes i.e. orally and topically (nasal, aural and eye preparations) (see sections 4.3 and 4.5)

Patients should be advised not to take other paracetamol-containing medicines concurrently.

The stated dose must not be exceeded. Patients should seek immediate medical advice should in the event of overdosage, because of the risk of irreversible liver damage (see section 4.9).

A variety of allergic skin reactions, with or without systemic features such as bronchospasm, angioedema have been reported following use of pseudoephedrine (see section 4.8).

Hypersensitivity reactions, including skin rashes, angioedema and anaphylaxis have been reported very rarely with paracetamol (see section 4.8).

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 the product should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

This product may act as a cerebral stimulant giving rise to hyperpyrexia, tremor and epileptiform convulsions.

If any of the following occur, this product should be stopped:

- Hallucinations
- Restlessness
- Sleep disturbances

Use with caution in occlusive vascular disease.

4.5 Interaction with other medicinal products and other forms of interaction

Pseudoephedrine

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.

MAOIs and/or RIMAs: This medicine should not be given to patients treated with monoamine inhibitors or within 14 days of stopping treatment as there is an increased risk of hypertensive crisis.

Moclobemide: risk of hypertensive crisis

Concomitant use of this medicine with tricyclic antidepressants (TCAs) or with sympathomimetic agents (such as appetite suppressants and amphetamine-like psychostimulants) may cause a rise in blood pressure.

Concomitant use of this medicine with anticholinergic drugs (such as TCAs) may enhance their effects.

The antibiotic furazolidone is a monoamine oxidase inhibitor. Therefore it should not be taken with this medicine (see Section 4.3).

Pseudoephedrine may antagonise the hypotensive action of antihypertensive drugs which interfere with sympathetic activity including bretylium, bethanidine, reserpine, guanethidine, debrisoquine, methyldopa, adrenergic neurone blockers - and beta- blockers (see sections 4.3 and 4.4).

Because of its pseudoephedrine content, concomitant use of this medicine with oxytocin or cardiac glycosides may cause of a risk of hypertension or an increased risk of dysrhythmias, respectively.

When used concurrently with ergot alkaloids (ergotamine & methysergide), this product can increase the risk of ergotism.

Concurrent use with halogenated anaesthetic agents such as chloroform, cyclopropane, halothane, enflurane or isoflurane may provoke or worsen ventricular arrhythmias.

Paracetamol

Patients who have taken barbiturates, tricyclic antidepressants and alcohol may show diminished ability to metabolise large doses of paracetamol, the plasma half-life of which can be prolonged.

Alcohol can increase the hepatotoxicity of paracetamol overdose and may have contributed to the acute pancreatitis reported in one patient who had taken an overdose of paracetamol.

Chronic ingestion of anticonvulsants or oral steroid contraceptives induce liver enzymes and may prevent attainment of therapeutic paracetamol levels by increasing first pass metabolism or clearance.

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced

by cholestyramine.

Because of its paracetamol content, the anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of this medicine with increased risk of bleeding; occasional doses have little or no significant effect.

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.

Pregnancy

This medicine should not be used during pregnancy unless the potential benefit of treatment to the mother outweighs the possible risks to the developing foetus.

Paracetamol

When given to the mother in labelled doses, paracetamol crosses the placenta into the foetal circulation as early as 30 minutes after ingestion and is effectively metabolised by foetal sulphate conjugation.

Paracetamol has been in widespread use for many years without ill consequence. Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in recommended dosage, but patients should follow that advise of their doctor regarding its use.

Pseudoephedrine

Although pseudoephedrine has been in widespread use for many years without apparent ill consequence, there are no specific data on its use during pregnancy. Caution should therefore be exercised by balancing the potential benefit of treatment to the mother against any possible hazards to the developing foetus.

Breast-feeding

This medicine should not be used during lactation unless the potential benefit of treatment to the mother outweighs the possible risks to the nursing infant.

Paracetamol

Paracetamol is excreted in breast milk in low concentrations (0.1% to 1.85% of the ingested maternal dose).

Pseudoephedrine

Pseudoephedrine distributes into and is concentrated in breast milk.

Fertility

There is no information on the effects of this medicine on human fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No special comment - unlikely to produce an effect.

4.8 Undesirable effects

The safety of pseudoephedrine and paracetamol combination from clinical trial data is based on one randomised, placebo-controlled trial in the management of symptoms attributed to the paranasal sinus associated with the common cold. In addition there were 12 randomised, placebo-controlled trials with single ingredient pseudoephedrine.

Adverse drug reactions identified during clinical trials and post-marketing experience with paracetamol, pseudoephedrine, or the combination are listed below by System Organ Class (SOC).
The frequencies are defined according to the following convention:

- Very common ≥1/10
- Common ≥1/100 and < 1/10
- Uncommon ≥1/1,000 and <1/100
- Rare ≥1/10,000 and <1/1,000
- Very rare <1/10,000
- Not known (cannot be estimated from the available data)

ADRs are presented by frequency category based on 1) incidence in adequately designed clinical trials or epidemiology studies, if available, or 2) when incidence cannot be estimated, frequency category is listed as ‘Not known’.

<i>System Organ Class (SOC)</i>	<i>Product</i>	<i>Frequency</i>	<i>Adverse Drug Reaction (Preferred Term)</i>
Blood and the lymphatic system disorders	<i>Paracetamol</i>	<i>Not known</i>	<i>Agranulocytosis</i> <i>Haemolytic anaemia</i> <i>Thrombocytopenic purpura</i>
Immune system disorders	<i>Paracetamol</i>	<i>Not known</i>	<i>Anaphylactic reaction</i>
	<i>Pseudoephedrine and Paracetamol</i>	<i>Not known</i>	<i>Hypersensitivity (cross-sensitivity may occur with other sympathomimetics)</i>
Psychiatric disorders	<i>Pseudoephedrine</i>	<i>Common</i>	<i>Insomnia</i> <i>Nervousness</i>
	<i>Pseudoephedrine</i>	<i>Rare</i>	<i>Hallucination</i>
	<i>Pseudoephedrine</i>	<i>Not known</i>	<i>Agitation</i> <i>Anxiety</i> <i>Delusion</i> <i>Euphoric mood</i> <i>Irritability</i> <i>Restlessness</i> <i>Sleep disorder</i>
Nervous system disorders	<i>Pseudoephedrine</i>	<i>Very common</i>	<i>Headache</i>
	<i>Pseudoephedrine</i>	<i>Common</i>	<i>Dizziness</i>
	<i>Pseudoephedrine</i>	<i>Not known</i>	<i>Psychomotor hyperactivity</i>
Cardiac disorders	<i>Pseudoephedrine</i>	<i>Not known</i>	<i>Arrhythmia</i> <i>Palpitations</i> <i>Tachycardia</i>
Vascular disorders	<i>Pseudoephedrine</i>	<i>Not known</i>	<i>Hypertension</i>
Gastrointestinal disorders	<i>Pseudoephedrine</i>	<i>Common</i>	<i>Dry mouth</i> <i>Nausea</i>
	<i>Pseudoephedrine / Paracetamol combination</i>	<i>Not known</i>	<i>Abdominal pain</i> <i>Diarrhoea</i>

	<i>Pseudoephedrine</i>		<i>Vomiting</i>
<i>Hepato-biliary disorders</i>	<i>Paracetamol</i>	<i>Not known</i>	<i>Hepatic function abnormal</i> <i>Hepatic necrosis</i>
<i>Skin and subcutaneous tissue disorders</i>	<i>Pseudoephedrine / Paracetamol combination</i>	<i>Not known</i>	<i>Angioedema</i> <i>Pruritus</i>
	<i>Pseudoephedrine and Paracetamol</i>		<i>Rash</i> <i>Rash pruritic</i>
	<i>Paracetamol</i>		<i>Urticaria</i>
<i>Renal and urinary disorders</i>	<i>Paracetamol</i>	<i>Uncommon</i>	<i>Nephropathy toxic</i>
	<i>Pseudoephedrine</i>	<i>Not known</i>	<i>Dysuria</i> <i>Urinary retention (in men - prostatic enlargement could have been an important predisposing factor)</i>
	<i>Paracetamol</i>		<i>Renal papillary necrosis (after prolonged administration)</i>
<i>General disorders and administration site conditions</i>	<i>Pseudoephedrine</i>	<i>Not known</i>	<i>Feeling jittery</i>
<i>Investigations</i>	<i>Paracetamol</i>	<i>Not known</i>	<i>Transaminases increased</i>
<i>Social circumstances</i>	<i>Paracetamol</i>	<i>Not known</i>	<i>Overdosage</i>

Liver damage has been reported after daily ingestion of excessive amounts. A review of a group of patients with chronic active hepatitis failed to reveal differences in the abnormalities of liver function in those who were long-term users of paracetamol nor was the control of their disease improved after paracetamol withdrawal.

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.

A variety of allergic skin reactions, with or without systemic features such as bronchospasm, angioedema have been reported following use of pseudoephedrine.

Hypersensitivity reactions, including skin rashes, angioedema and anaphylaxis have been reported very rarely with paracetamol.

Very rare cases of serious skin reactions have been reported.

Reporting of Suspected Adverse Reactions.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Paracetamol

Please refer to local guidance for the treatment of paracetamol overdose.

Liver damage is likely in adults and adolescents who have taken 7.5 to10 g or more of paracetamol 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 g. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

Ingestion of 5 g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk Factors:

If the patient

a, Is on long term treatment with carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St John’s Wort or other drugs that induce liver enzymes.

Or

b, Regularly consumes ethanol in excess of recommended amounts.

Or

c, Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms

Symptoms of paracetamol overdose usually occur within the first 24 hours and are pallor, hyperhidrosis, malaise, nausea, vomiting, anorexia and abdominal pain. Liver damage may not become apparent until 48 to 72 hours after ingestion. This may include hepatomegaly, liver tenderness, jaundice, acute hepatic failure and hepatic necrosis. Blood bilirubin, hepatic enzymes, INR, prothrombin time, blood phosphate and blood lactate may be increased. These clinical events associated with paracetamol overdose are considered expected, including fatal events due to fulminant hepatic failure or its sequelae.

The following sequelae to acute hepatic failure associated with paracetamol overdose (adults and adolescents: ≥ 12 years of age :> 7.5 g within 8 hours) are considered expected and may be fatal.

Expected Sequelae to Acute Hepatic Failure Associated with Paracetamol Overdose

System Organ Class (SOC)	Adverse event
Infections and infestations	Bacterial infection Fungal infection Sepsis
Blood and lymphatic system disorders	<i>Coagulopathy</i> <i>Disseminated intravascular coagulation</i> <i>Thrombocytopenia</i>
Metabolism and nutrition disorders	Hypoglycaemia Hypophosphatemia Lactic acidosis Metabolic acidosis
Nervous system disorders	Cerebral oedema Coma (with massive paracetamol overdose or multiple drug overdose) Encephalopathy
Cardiac disorders	Cardiomyopathy Cardiac arrhythmias

Vascular disorders	Hypotension
Respiratory, thoracic and mediastinal disorders	Respiratory failure
Gastrointestinal disorders	Gastrointestinal haemorrhage Pancreatitis
Renal and urinary disorders	Acute renal failure*
General disorders and administration site conditions	Multi-organ failure

*Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may also develop even in the absence of severe liver damage.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with the local centres and/or experts that provide advice on poisons and overdoses or a liver unit.

Pseudoephedrine

Symptoms

Overdosage may result in:
Metabolism and nutrition disorders: hyperglycaemia, hypokalaemia
Psychiatric disorders: CNS stimulation, insomnia; irritability, restlessness, anxiety, agitation; confusion, delirium, hallucinations, psychoses
Nervous system disorders: convulsions, tremor, intracranial haemorrhage including intracerebral haemorrhage, drowsiness in children
Eye disorders: mydriasis
Cardiac disorders: palpitations, tachycardia, reflex bradycardia, supraventricular and ventricular arrhythmias, dysrhythmias, myocardial infarction
Vascular disorders: hypertension, hypertensive crisis
Gastrointestinal disorders: nausea, vomiting, ischaemic bowel infarction
Musculoskeletal and connective tissue disorders: rhabdomyolysis
Renal and urinary disorders: acute renal failure, difficulty in micturition

Management

Measures should be taken to maintain and support respiration and control convulsions. Gastric lavage should be performed if indicated. Catheterisation of the bladder may be necessary. If desired, the elimination of pseudoephedrine can be accelerated by acid diuresis or by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: R01BA02

Pseudoephedrine has direct and indirect sympathomimetic activity and is an effective upper respiratory tract decongestant. Pseudoephedrine is substantially less potent than ephedrine in producing both tachycardia and elevation in systolic blood pressure and considerably less potent in causing stimulation of the central nervous system.

ATC Code: N02BE01

Paracetamol has analgesic and antipyretic actions but only weak anti-inflammatory properties. This may be explained by the presence of cellular peroxides at sites of inflammation which prevent inhibition of cyclo-oxygenase by paracetamol at other sites associated with low levels of cellular peroxides, eg pain, fever, paracetamol and successfully inhibit prostaglandin biosynthesis.

5.2 Pharmacokinetic properties

Pseudoephedrine

Pseudoephedrine is partly metabolised in the liver by N-demethylation to norpseudoephedrine, an active metabolite. Pseudoephedrine and its metabolite are excreted in the urine: 55% to 75% of a dose is excreted unchanged. The rate of urinary excretion of pseudoephedrine is accelerated when the urine is acidified. Conversely as the urine pH increases, the rate of urinary excretion is slowed.

In a limited study, three mothers nursing healthy infants were given an antihistamine-decongestant preparation containing 60 mg of pseudoephedrine and 2.5 mg of triprolidine. Milk concentrations of pseudoephedrine were higher than plasma levels in all three patients, with peak milk concentrations occurring at 1.0–1.5 hours. The investigators calculated that 1000 ml of milk produced during 24 hours would contain approximately 0.5%–0.7% of the maternal dose. However, following a single-blind, crossover study of a single dose of pseudoephedrine 60 mg vs. placebo conducted in 8 lactating mothers, and assuming maternal intake of 60 mg pseudoephedrine hydrochloride four times daily, the estimated infant dose of pseudoephedrine based on AUC and an estimated milk production rate of 150 ml/kg/day was 4.3% (95% CI, 3.2, 5.4%; range 2.2 to 6.7%) of the weight-adjusted maternal dose.

Paracetamol

Peak plasma paracetamol concentration usually occurs between 30 and 90 minutes after oral ingestion. Paracetamol is distributed uniformly throughout most body fluids and is only 15 to 25 per cent bound to plasma proteins. The plasma half life of paracetamol after therapeutic doses is in the range of 1 to 3 hours.

5.3 Preclinical safety data

Mutagenicity

Paracetamol

In vivo mutagenicity tests of paracetamol in mammals are limited and show conflicting results. Therefore, there is insufficient information to determine whether paracetamol poses a mutagenic risk to man.

Paracetamol has been found to be non-mutagenic in bacterial mutagenicity assays, although a clear clastogenic effect has been observed in mammalian cells *in vitro* following exposure to paracetamol (3 and 10 mM for 2 hr).

Pseudoephedrine

The results of a wide range of tests indicate that pseudoephedrine does not pose a mutagenic risk to man.

Carcinogenicity

Paracetamol

There is inadequate evidence to determine the carcinogenic potential of paracetamol in humans. A positive association between the use of paracetamol and cancer of the ureter (but not of other sites of the urinary tract) was observed in a case-control study in which approximate lifetime consumption of paracetamol (whether acute or chronic) was estimated.

However, other similar studies have failed to demonstrate statistically significant association between paracetamol and cancer of the urinary tract, or paracetamol and renal cell carcinoma.

There is limited evidence for the carcinogenicity of paracetamol in experimental animals. Liver cell tumours can be detected in mice and liver and bladder carcinomas can be detected in rats, following chronic feeding 500 mg/kg/day paracetamol.

Pseudoephedrine

There is insufficient information available to determine whether pseudoephedrine has carcinogenic potential.

Teratogenicity

Paracetamol

There is no information relating to the teratogenic potential paracetamol. In humans, paracetamol crosses the placenta and attains concentrations in the foetal circulation similar to those in the maternal circulation. Intermittent maternal ingestion of therapeutic doses of paracetamol is not associated with teratogenic effects in humans. Paracetamol has been found to be fetotoxic to cultured rat embryos.

Pseudoephedrine

Systemic administration of pseudoephedrine, up to 50 times the human daily dosage in rats and up to 35 times the human daily dosage in rabbits did not produce teratogenic effects.

Fertility

Paracetamol

There is no information relating to the effects of paracetamol on human fertility. A significant decrease in testicular weight was observed when male Sprague-Dawley rats were given daily high doses of paracetamol (500 mg/kg body weight/day) orally for 70 days.

Pseudoephedrine

Systemic administration of pseudoephedrine to rats, up to 7 times the human daily dosage in females and 35 times the human daily dosage in males, did not impair fertility or alter foetal morphological development and survival.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Pregelatinised maize starch
Crospovidone
Sodium Starch Glycolate (type A)
Povidone
Stearic acid
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25°C. Store in the original package.

6.5 Nature and contents of container

Opaque white PVC and PVDC/Aluminium foil blister.
Packs of 4, 12, 15 and 24 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

McNeil Healthcare (Ireland) Ltd.
Airton Road
Tallaght
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA0823/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 February 1998

Date of last renewal: 06 February 2008

10 DATE OF REVISION OF THE TEXT

March 2016