

NEW ZEALAND DATA SHEET

NEULIN™-SR

1 PRODUCT NAME

NUELIN-SR 250 mg sustained release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains theophylline BP 250 mg.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Sustained release tablet.

White, round, biconvex tablets marked **250** on one face and no markings on the other face.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

NUELIN-SR tablets are indicated for the relief and prophylaxis of reversible bronchospasm associated with asthma, chronic bronchitis and emphysema.

4.2 Dose and method of administration

Desirable therapeutic levels are considered to be between 10-20 µg/mL (55-110 µmol/L). Higher levels may produce toxic effects. Toxic effects may also occur at therapeutic levels. When maximum response is required, dose levels should be individually titrated. Serum theophylline may be monitored to confirm that levels are within the therapeutic range. Monitoring is recommended, in particular when dose levels exceed 1g daily in adults or 24 mg/kg daily in children.

NUELIN-SR doses should be adjusted for factors known to affect theophylline clearance (see sections 4.4 and 4.5).

Dose

Adults: 13 mg/kg per 24 hours.

Paediatric Population

Children over 2 years: Starting dose 16 mg/kg every 24 hours to a mean 20 mg/kg every 24 hours.

Children under 2 years: Not to be given except on the advice of a physician.

Children (from 6 months to 16 years) have a more rapid clearance of theophylline resulting in the need for higher per kg doses.

Special Populations

Where possible patients should be commenced on a lower dose and gradually increased to the maintenance dose to minimise the incidence of side effects. Extra caution is required with the elderly as they may have slower clearance rates. Obese patients should be dosed on the basis of ideal rather than actual body weight. Smokers often require higher doses than non-smokers due to more rapid clearance of theophylline.

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Method of Administration

NUELIN-SR tablets are to be taken with a full glass of water, preferably with food every 12 hours. The tablets are not to be divided, chewed or crushed.

4.3 Contraindications

Hypersensitivity to the active ingredient or to any excipients listed in section 6.1 or to xanthines.

4.4 Special warnings and precautions for use

Theophylline monitoring

As there is a correlation between plasma levels of theophylline and therapeutic effect, and as patient response can vary considerably due to variable rates of elimination, monitoring plasma levels in individual patients is strongly recommended.

If side effects appear or if unusually high doses are required, serum theophylline should be monitored. Blood samples for monitoring should be drawn immediately before administration of the morning dose when the serum theophylline level is lowest. Another sample should be drawn 5-10 hours after administration of NUELIN when the theophylline level is at a maximum.

Dosage should be individualised if optimal therapeutic effect is to be achieved. However, individual patients also have a widely variable tolerance to adverse effects and so symptomatology should be considered as well as monitored levels.

There is some evidence that theophylline exhibits dose-dependent kinetics, at least in sick and elderly patients. Care should be exercised by titration of dosage requirements in small increments and by monitoring serum theophylline levels.

Management of acute asthma attacks

Acute symptoms of asthma require rapid treatment: Sustained release products are therapeutically inappropriate for acute asthma requiring prompt treatment.

Xanthine derivatives

Theophylline should not be administered concurrently with other xanthine medications.

Theophylline clearance

Theophylline clearance decreases in patients with reduced thyroid function, congestive heart failure, acute pulmonary oedema, chronic obstructive pulmonary disease, severe hypoxia, pneumonia, acute febrile episodes and during acute viral infection. Clearance is markedly decreased in patients with impaired liver function, such as hepatic cirrhosis (see section 4.5).

Certain substances, including tobacco and marijuana, have been shown to affect the hepatic clearance of theophylline, thereby affecting its serum concentration (see section 4.5). It is recommended that serum theophylline levels are monitored and dosage adjustments made if concomitant therapy with these drugs/substances is commenced or ceased during continued theophylline therapy.

Cardiac disorders

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Because of its cardiac side effects, use theophylline with caution in patients with cardiac arrhythmias, coronary artery disease, unstable angina, cardiomyopathy and severe hypertension. Theophylline increases gastric acid secretion and should be used with caution in patients with peptic ulcer or gastro-oesophageal reflux.

4.5 Interaction with other medicines and other forms of interaction

The following drugs have been shown to decrease the hepatic clearance of theophylline, thus increasing its serum concentration: Cimetidine, high dose allopurinol, propranolol, macrolide antibiotics (e.g. erythromycin, clarithromycin) quinolone antibiotics (e.g. ciprofloxacin and enoxacin), alcohol, oral contraceptives, mexilitene, tacrine, thiabendazole, disulfiram, Interferon alpha and verapamil.

The following substances have been shown to increase the hepatic clearance of theophylline, thus lowering its serum concentration: tobacco or marijuana smoking, phenobarbitone, phenytoin, carbamazepine and rifampicin. Theoretical potential interactions of theophylline with products containing *Hypericum perforatum* (St John's wort), possibly involving the CYP 1A2 isoform, could result in reduced plasma levels of theophylline. It is recommended that serum theophylline levels are monitored and dosage adjustments made if concomitant therapy with these drugs/substances is commenced or ceased during continued theophylline therapy.

Ventricular arrhythmias have been reported when halothane is used concurrently with theophylline. Concurrent use of ketamine with theophylline may lower the seizure threshold. Theophylline has been reported to enhance the renal clearance of lithium, thus reducing serum lithium levels.

Synergism with adrenaline and other sympathomimetic amines has been reported with theophylline. Caution should be exercised when sympathomimetic agents are also part of the regimen.

Concomitant administration of a β -adrenergic agonist with methylxanthines has resulted in cardiac arrhythmias and sudden death in studies carried out in laboratory animals. The clinical significance of these findings when applied to humans is not known at present.

The effect of ranitidine, diltiazem, nifedipine, isoniazid, frusemide, influenza vaccine and corticosteroids on theophylline is uncertain, but concomitant use of these drugs should be monitored closely.

Laboratory test interactions

Xanthine containing beverages (e.g. tea, coffee, cola, cocoa) may interfere with some serum theophylline assays.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category A

Although theophylline has a Category A rating, it does cross the placental barrier. The effect on foetal development is not known. Theophylline clearance is significantly decreased in premature

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infants. Therefore, if this drug is administered to the mother near the time of delivery, the neonate should be monitored closely for the pharmacological effects of theophylline. Hence the use of theophylline in pregnant women should be balanced against the risk of uncontrolled asthma.

Lactation

Theophylline is secreted in breast milk and irritability has been reported in infants of nursing mothers taking theophylline. It is advisable to keep serum theophylline concentrations as low as possible in nursing mothers while maintaining adequate asthma control.

4.7 Effects on ability to drive and use machines

NEULIN-SR does not affect the ability to drive or operate machinery.

4.8 Undesirable effects

The most common adverse reactions are gastric irritation, nausea, vomiting, anorexia, epigastric pain, reactivation of peptic ulcer, gastro-oesophageal reflux, haematemesis, tachycardia, palpitation, headache, CNS stimulation, reflex hyperexcitability, insomnia and tremor.

Other possible reactions include diarrhoea, extrasystoles, flushing, hypotension, tachypnoea, potentiation of diuresis, albuminuria, haematuria, rash, hyperglycaemia, hypokalaemia, alopecia and inappropriate ADH secretion (high dose).

More serious signs of high serum levels (usually above 30 µg/mL), such as cardiac arrhythmias and convulsions, may appear rarely without prior warning.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

See also section 4.8 for possible drug effects that may be seen in overdose.

Symptoms

Early symptoms of toxicity such as anorexia, nausea, vomiting, headache, irritability, agitation, anxiety, insomnia, hypotension, palpitations and tachycardia, may progress to sensory disturbances, confusion, hyperthermia, ventricular arrhythmias, extreme thirst, delirium and convulsions.

Every theophylline overdose should be regarded as potentially fatal and all patients should be closely monitored.

Treatment

There is no specific antidote to theophylline. Symptomatic support is indicated. Gastric lavage and general supportive measures (e.g. to maintain circulation, respiration and fluid and electrolyte balance) are recommended. Oral activated charcoal may reduce serum theophylline levels, whilst in severe cases charcoal haemoperfusion may be required.

The important features of overdose management are:

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Gastric Decontamination

Gastric lavage is recommended especially when slow release preparations have been ingested. Note that the conscious state, gag reflex or occurrence of seizures may require the patient to be intubated before lavage is carried out. (Ipecac-induced emesis is not appropriate because it reduces the likelihood that patients will be able to tolerate oral charcoal.)

Use of Activated Charcoal and Cathartic (either sorbitol or polyethylene glycol)

This has been shown in several studies to reduce the half-life of theophylline substantially, even when absorption has been completed. The recommended dose is 1 g/kg every 4-6 hours (or 10 g/hour) until the theophylline level has plateaued or commenced falling or is below 55 µmol/L. (This depends on the experience of the physician in managing theophylline overdose.)

Control of Emesis (otherwise patients will not tolerate charcoal)

Metoclopramide, ranitidine, droperidol and possibly ondansetron can be used but there is no controlled trial evidence for any of these.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: drugs for obstructive airway disease. ATC code: R03DA04.

Theophylline has a direct relaxant effect on the smooth muscle of bronchial airways and pulmonary blood vessels, serving as a bronchodilator and pulmonary vasodilator. It also exhibits activities typical of xanthines such as CNS stimulation including the respiratory centre, cardiac stimulation, coronary vasodilatation, diuresis and increased gastric secretion.

The mechanism of action of theophylline *in vivo* has not been fully elucidated. It is believed to mediate smooth muscle relaxation by inhibition of phosphodiesterase, thus reducing intracellular hydrolysis of cyclic AMP. Increased cellular concentrations of cAMP have been associated with relaxation of bronchial smooth muscle.

There is no evidence that tolerance develops with continued use of theophylline.

Theophylline is closely related to other xanthines, caffeine and theobromine. Generally the xanthines relax smooth muscle, act on the kidney to produce diuresis, and stimulate the central nervous system and cardiac muscle.

5.2 Pharmacokinetic properties

NEULIN-SR is a sustained release formulation appropriate for long term use. Steady-state conditions are usually achieved after four days' therapy. Following administration of NEULIN-SR 500 mg every 12 hours a mean steady-state plasma concentration of 14.3 µg/mL was observed. NEULIN-SR tablets were shown to be bioequivalent when administered in equal doses (500 mg every 12 hours), whether given as 4 tablets of NEULIN-SR 125 mg, 2 tablets of NEULIN-SR 250 mg or 1 tablet of NEULIN-SR 500 mg. The rate and the extent of absorption of theophylline from each of the NEULIN-SR tablet sizes is equivalent.

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It is now generally believed that plasma concentrations of 10-20 µg/mL constitute a therapeutic range, although some patients may benefit from levels below this.

Absorption

Theophylline is well absorbed throughout the gastrointestinal tract. The bioavailability of theophylline from NUELIN-SR is approximately 100 %. Peak levels after administration of NUELIN-SR usually occur at 4 to 6 hours post-dose.

Total bioavailability is not altered by food intake. Single dose studies with NUELIN-SR show that food delays the rate of absorption slightly, especially in children. In multiple dosing situations a slower rate of theophylline absorption leads to lower peak-trough fluctuation.

The plasma half-life of theophylline in adults varies considerably. In healthy adults it ranges from 3 to 12 hours. The half-life is shortened by smoking and is prolonged by reduced hepatic function, congestive heart failure, pulmonary disease, severe hypoxia, reduced thyroid function, acute febrile states, viral infections and administration of some drugs (see section 4.5). Patients with a prolonged half-life of theophylline, from whatever cause, require a reduced dose.

In children aged 1-9 years, the half-life is usually significantly shorter than in adults, averaging about 3.5 hours.

Distribution

Approximately 50-70 % of circulating theophylline is bound to the plasma proteins of adults, but binding is decreased to about 40 % in newborn infants and in adults with hepatic cirrhosis. Theophylline partitions into saliva and breast milk and crosses the placental barrier.

Metabolism

Theophylline is metabolised in the liver to 1,3-dimethyluric acid, 1-methyluric acid and 3-methylxanthine. 3-Methylxanthine has some pharmacological activity, but less than theophylline.

Excretion

Theophylline and its metabolites are excreted by the kidney. About 10 % of the administered dose is excreted unchanged.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Guar gum

Magnesium stearate

The tablet formulation is sugar-free and does not contain gluten.

6.2 Incompatibilities

None known

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6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30°C. Keep container tightly closed

6.5 Nature and contents of container

Blister pack, PVC/PVDC: 100 tablets

Bottle, plastic, HDPE: 100 tablets*

*Not marketed

6.6 Special precautions for disposal

No special requirements for disposal.

7 MEDICINE SCHEDULE

Prescription

8 SPONSOR

iNova Pharmaceuticals (New Zealand) Limited

c/- Simpson Grierson

88 Shortland Street,

Auckland 1141

Toll free number: 0508 375 394

9 DATE OF FIRST APPROVAL

1 August 1979

10 DATE OF REVISION OF THE TEXT

7 February 2018

SUMMARY TABLE OF CHANGES

Date	Change
7 February 2018	Data sheet reformatted Section 4.3. Editorial changes to text Section 4.5: Moved- Xanthine containing beverages (e.g. tea, coffee, cola, cocoa) may interfere with some serum theophylline assays from section 4.4 to 4.5 under the sub-heading <u>Laboratory test interactions.</u> Section 5.1: Added -_Pharmacotherapeutic group: drugs for obstructive airway disease. ATC code: R03DA04. Section 6.5: Description expanded to be

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	consistent with the TPDR Section 8: Sponsor name and address changed
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