

**AUSTRALIAN PRODUCT INFORMATION –  
NUELIN®-SR (THEOPHYLLINE) TABLETS and  
NUELIN® (THEOPHYLLINE) SYRUP**

## **1 NAME OF THE MEDICINE**

Theophylline.

## **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Nuelin-SR Tablets contain 200 mg, 250 mg or 300 mg anhydrous theophylline in the form of sustained release tablets. Nuelin-SR Tablets also contain guar gum, magnesium stearate and purified water.

Nuelin Syrup contains 133.3 mg anhydrous theophylline per 25 mL in immediate release form. Nuelin Syrup also contains methyl hydroxybenzoate, propyl hydroxybenzoate, sorbitol, berry citrus flavouring, sucrose and purified water.

## **3 PHARMACEUTICAL FORM**

NUELIN SR 200 theophylline 200mg tablet bottle – white round biconvex tablet N/L on one side and 200 on the other.

NUELIN SR 250 theophylline 250mg tablet bottle – white, round biconvex tablets marked N/L 250.

NUELIN SR 300 theophylline 300mg tablet bottle – white round biconvex tablet N/L on one side and 300 on the other.

NUELIN Syrup theophylline 26.67mg/5mL bottle – clear liquid, berry flavour.

## **4 CLINICAL PARTICULARS**

### **4.1 THERAPEUTIC INDICATIONS**

For the relief and prophylaxis of reversible bronchospasm associated with bronchial asthma, bronchitis, emphysema and related conditions.

### **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 particularly recommended when dose levels exceed 1 g daily in adults or 24 mg/kg daily in children.

Appropriate dosage adjustments should be made for smoking, heart failure, acute pulmonary oedema, chronic alcohol ingestion, established hepatic cirrhosis, severe airways obstruction, severe pneumonia, severe hypoxia, thyroid function, adolescence (12-18 years), children (8-12 years) and concomitant use of interacting drugs. (See section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Children have rapid clearance of theophylline and may require a dosage increase that should be controlled by measurement of serum theophylline.

#### Elderly

In patients aged over 65 years theophylline clearance is decreased by approximately 25 %.

## **Nuelin-SR Tablets**

### **Adults**

200 to 300 mg (one tablet) every twelve hours. This dose can be gradually increased or decreased by half a tablet if sufficient therapeutic effect is not achieved or if side effects occur.

### **Children**

Nuelin-SR Tablets are not recommended for administration to children under 2 years of age.

For children over 2 years, administration as advised by the physician. The daily dose should be adjusted according to bodyweight, usually on the basis of up to 10 mg/kg bodyweight every twelve hours. As a guideline, a child from 12 kg to 25 kg bodyweight (2-7 years) usually requires 125 mg bid (twice a day) and a child over 25 kg, 250 mg bid (twice a day)

Note: For children taking Nuelin-SR tablets, Nuelin Syrup may be considered as an alternative.

**NOTE: Nuelin-SR Tablets should be taken every twelve hours. On no account should the tablets be chewed or crushed.**

## **Nuelin Syrup**

Not recommended for children under 2 years except on the advice of a doctor.

<b>Age</b>	<b>Average Weight</b>	<b>Dose every 6 hours</b>
Children 2-4 years:	12-16 kg	10-15 mL
Children 4-6 years:	16-20 kg	15-20 mL
Children 6-12 years:	20-41 kg	20-25 mL
Adults & Children over 12 years:	Over 41 kg	25 mL

Nuelin Syrup is best taken an hour before meals with a glass of water, or if necessary with or immediately after meals to lessen gastro-intestinal irritation.

### **4.3 CONTRAINDICATIONS**

Nuelin-SR Tablets and Nuelin Syrup should not be used where hypersensitivity to its constituents or to xanthines generally is known or has been demonstrated.

### **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

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 (see THEOPHYLLINE MONITORING in section 4.9 OVERDOSE). 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.

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

Theophylline should not be administered concurrently with other xanthine medications and caution should be exercised when sympathomimetic agents are also part of the regimen.

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.

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.

Smoking may increase theophylline clearance and increased doses of theophylline may be required. (See section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)

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

#### **Use in hepatic impairment**

Clearance is markedly decreased in patients with impaired liver function, such as hepatic cirrhosis (See section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

#### **Use in the elderly**

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.

#### **Paediatric use**

*No data available.*

#### **Effects on laboratory tests**

*No data available.*

### **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

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 (eg. erythromycin, clarithromycin) quinolone antibiotics (eg. 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. Concomitant administration of a  $\beta$ -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.

#### **4.6 FERTILITY, PREGNANCY AND LACTATION**

##### **Effects on fertility**

*No data available.*

##### **Use in pregnancy – 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 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.

##### **Use in lactation**

Theophylline is excreted 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**

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

#### **4.8 ADVERSE EFFECTS (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  $\mu\text{g/mL}$ ), such as cardiac arrhythmias and convulsions, may appear rarely without prior warning.

##### **Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration 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 at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

#### **4.9 OVERDOSE**

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

**See also section 4.8 ADVERSE EFFECT (UNDESIRABLE EFFECTS) for possible drug effects that may be seen in overdosage.**

## 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 (eg 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:

### 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.

### **Theophylline Monitoring** (See also section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

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 SR when the theophylline level is at a maximum

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

#### **Mechanism of action**

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. One mechanism of smooth muscle relaxation may be inhibition of phosphodiesterase that reduces intracellular hydrolysis of cyclic AMP. Increased intracellular concentrations of cyclic AMP have been associated with relaxation of bronchial smooth muscle.

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

### Relationship to Other Drugs

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

### **Clinical trials**

*No data available.*

## **5.2 PHARMACOKINETIC PROPERTIES**

Nuelin-SR Tablets are a sustained release formulation appropriate for long term use. Steady-state conditions are usually achieved after 4 days' therapy.

Nuelin Syrup is an immediate release formulation.

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 Tablets is approximately 100 %. Peak levels after administration of Nuelin-SR Tablets usually occur at 4 to 6 hours post-dose. Total bioavailability is not altered by food intake. Single dose studies with Nuelin-SR Tablets 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.

Peak plasma theophylline levels occur 1.5 to 2 hours after a dose of Nuelin Syrup.

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.

The half-life of theophylline 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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS) Patients with a prolonged half-life of theophylline, from whatever cause, require a reduced dosage.

In children aged 1-9 years, the half-life is usually significantly shorter than in adults, averaging about 3.5 hours. In newborns and neonates, clearance is extremely slow.

### **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, principally to 1,3-dimethyluric acid with other metabolites being 3-methylxanthine and 1-methyluric acid. 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 in the urine.

### 5.3 PRECLINICAL SAFETY DATA

#### Genotoxicity

No data available.

#### Carcinogenicity

No data available.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

Refer to Section 2 - Qualitative and quantitative composition.

### 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

### 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

### 6.5 NATURE AND CONTENTS OF CONTAINER

**Nuelin SR Tablets:** HDPE bottle, 100's

**Nuelin Syrup:** Amber PET bottle; 500 mL, 100 mL\*, 5 L\*

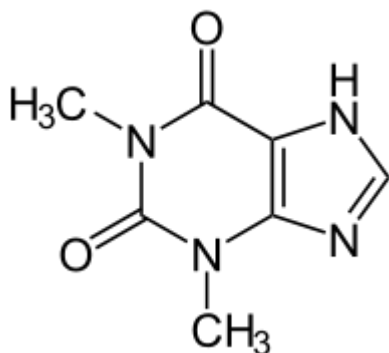
\* - Not Marketed

### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

### 6.7 PHYSICOCHEMICAL PROPERTIES

#### Chemical structure



Chemical name: 1,3-Dimethylxanthine, 2,6-Dihydroxy-1,3-dimethylpurine, 3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione.

Molecular formula is C<sub>7</sub>H<sub>8</sub>N<sub>4</sub>O<sub>2</sub> (molecular weight 180.16)

**CAS number:** 58-55-9

## **7 MEDICINE SCHEDULE (POISONS STANDARD)**

Nuelin-SR Tablets: (S4) Prescription Only Medicine

Nuelin Syrup: (S3) Pharmacist Only Medicine

## **8 SPONSOR**

iNova Pharmaceuticals (Australia) Pty Limited

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Chatswood NSW 2067

Toll Free: 1800 630 056

## **9 DATE OF FIRST APPROVAL**

**Nuelin-SR 200 mg Tablets:** 16 May 1997

**Nuelin-SR 250 mg Tablets:** 11 August 1993

**Nuelin-SR 300 mg Tablets:** 16 May 1997

**Nuelin Syrup:** 4 July 1991

## **10 DATE OF REVISION**

8 January 2019

### **SUMMARY TABLE OF CHANGES**

<b>Section Changed</b>	<b>Summary of new information</b>
All	Transfer of text from old PI format (without changes)
All	Reformatting of approved PI (Dec 2018)