

A horizontal dimension line with arrows at both ends, indicating a length of 140mm. The text "140mm" is centered above the line.

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NUELIN[®] SR TABLETS

PHARMACOLOGY

Site and Mode 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.

PHARMACOKINETICS

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 Drug 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.

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.

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

CONTRAINDICATIONS: Nuelin SR should not be used where hypersensitivity to its constituents or to xanthines generally is known or has been demonstrated.

1. 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). 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.

2. Acute symptoms of asthma requiring rapid treatment: Sustained release products are therapeutically inappropriate for acute asthma requiring prompt treatment.
3. Theophylline should not be administered concurrently with other xanthine medications and caution should be exercised when sympathomimetic agents are also part of the regimen.
4. 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. Also refer to Drug Interactions section.
5. 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.
6. Smoking may increase theophylline clearance and increased doses of theophylline may be required. (See Drug Interactions.)
7. 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.
8. Xanthine containing beverages (eg tea, coffee, cola, cocoa) may interfere with some serum theophylline assays.

Use in Pregnancy: Theophylline 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.

Drug 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, mexiletine, 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, phenobarbital, 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 be 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.

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200mm

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PRODUCT	PRINTER DETAILS	COLOURS	FONTS	AMENDS	ARTWORKER INFO
Brand: Nuelin	Dieline Ref: XXX	Black 	Fonts Used: Helvetica Bold Helvetica Bold Helvetica Condensed Medium Helvetica Condensed Bold Swiss 721 BT Myriad Pro Helvetica Condensed Oblique	27/04/18 : New Artwork Build - Elaine 12/07/18 : Text Amends - Sunny	Artwork Software: Illustrator CC 2017
Product Variant: Bronchodilator	Printer: XXX				
Pack Size: 500 Tablets	EMO: Adcock				
Country: SG, HK, LK	SKU No: 100074, 100084				Barcode %:
Filename: 81880_LT0028_Nuelin_Bronchodilator_500_Leaflet_SG_HK_LK_V1.ai	CODES				
Date: 12/07/2018	JOB NO: 81880		Body copy size: 6pts		APPROVALS
Component: Leaflet	VERSION: 1		Min. font size: 1.24mm		Artworker:
Dimensions: 140mm w x 200mm h	UIC: LT0028				Signed:
					Date: 00/00/2018

140mm

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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 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.

ADVERSE REACTIONS

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.

DOSAGE AND ADMINISTRATION

Desirable therapeutic levels are considered to be between 10-20 $\mu\text{g/mL}$ (55-110 $\mu\text{mol/L}$). 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.

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 is 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 and a child over 25 kg, 250 mg bid. 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 Drug 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%.

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

OVERDOSAGE: (See also ADVERSE REACTIONS 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 (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 $\mu\text{mol/L}$. (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 PRECAUTIONS.) 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.

PRESENTATION

Nuelin SR 125mg tablets (white, round, scored, marked 125 and N/L on reverse) 500's

Nuelin SR 200mg tablets (white, round, scored, marked 200 and N/L on reverse) 500's Hong Kong only

Nuelin SR 250mg tablets (white, round, scored, marked 250 and N/L on reverse) 500's

Nuelin SR 300mg tablets (white, round, scored, marked 300 and N/L on reverse) 500's Hong Kong only

STORAGE CONDITIONS

Store below 30°C. Keep container tightly closed.

SHELF LIFE

3 years

Manufactured in India

By Adcock Ingram Limited

No. 49 (C&D) Bommasandra Indl. Area,

Anekal Taluk, Bangalore - 560 099, India

Revision Date: January 2018

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PRODUCT	PRINTER DETAILS	COLOURS	FONTS	AMENDS	ARTWORKER INFO
Brand: Nuelin Product Variant: Bronchodilator Pack Size: 500 Tablets Country: SG, HK, LK Filename: 81880_LT0028_Nuelin_Bronchodilator_500_Leaflet_SG_HK_LK_V1.ai Date: 12/07/2018 Component: Leaflet Dimensions: 140mm w x 200mm h	Dieline Ref: XXX Printer: XXX EMO: Adcock SKU No: 100074, 100084 CODES JOB NO: 81880 VERSION: 1 UIC: LT0028	Black	Fonts Used: Helvetica Bold Helvetica Bold Helvetica Condensed Medium Helvetica Condensed Bold Swiss 721 BT Myriad Pro Helvetica Condensed Oblique Body copy size: 6pts Min. font size: 1.24mm	27/04/18 : New Artwork Build - Elaine 12/07/18 : Text Amends - Sunny	Artwork Software: Illustrator CC 2017 Barcode %: APPROVALS Artworker: Signed: Date: 00/00/2018