PHARMACODE POSITION

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TEXT MATTER

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PRODUCT INFORMATION

NUELIN SR TABLETS

COMPOSITION

Nuelin SR contains 125mg or 250mg anhydrous theophylline (1,3-dimethyl xanthine, also named 3,7-dihydro 1,3-dimethyl-purine-2,6(1H)-dione) in the form of sustained release 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 is not fully elucidated. It is believed to mediate smooth muscle relaxation by inhibition of phosphodiesterase, thus reducing intracellular hydrolysis of cyclic AMP. Theophylline also acts additively or synergistically with B2-adrenoceptor agonists such as catecholamines. These increase intracellular levels of cyclic AMP by stimulation of adenyl cyclase. The clinical significance of this interaction should be considered when theophylline is used concurrently with sympathomimetic agents.

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.

PHARMACOKINETICS

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

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.

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.

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.

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.

PRECAUTIONS

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, 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 B-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 µg/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 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.

ADULTS

250 mg 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 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 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) 100's

Nuelin SR 250mg tablets (white, round, scored, marked 250 and N/L on reverse) 100's

STORAGE CONDITIONS

Store below 30°C. Keep container tightly closed.

MANUFACTURER

Adcock Ingram Limited
No. 49 (C&D), Bommasandra
Industrial Area, Anekal Taluk,
Bangalore 560 099, INDIA

Revision date: May 2025 A10362

160mm BACK

PHARMACODE POSITION

260mm

A10362-NUELIN 125 MG and 250 MG SR TABLET 100 MY LT
Dimensions.: 160x260mm

RE-TYPESET ARTWORK. Due to the nature of the files received, this artwork has been re-typeset.

GROUP 24|7 WORLDWIDE™ inova pharmaceuticals

ARTWORK

Job No. : JB-03296 V3
UIC : A10362
SKU : 100358 100359

09.05.25 - V0 - Artwork build - Soravit
13.05.25 - V1 - Amend - Passanai
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A10362_NUELIN 125 MG and 250 MG SR TABLET 100
Component : LEAFLET
Country : MY

Dieline Ref: PP-9296
EMO: ADCOCK
Printer: Xxxxxx Xxxxxxxxxxx

G247 File Name: 108433_ A10362_NUELIN 125 MG and 250 MG SR TABLET 100_MY_LT_V3

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Guide

PLEASE NOTE

This HI RES PDF is not to be used as Final Artwork

Supplier information may be present on the packaging

EMO/Printing Vendor:

Please share the Artwork PDF to Printer for checks on:

- Colours - No. of colours, Sequence, CMYK/PMS
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Moving forward when possible any additonal information and technical check required by EMO on the Artwork BEFORE APPROVING.

2.00 mm Helvetica Bold Condensed 6.5 pt — **PRODUCT INFORMATION**
3.14 mm — **NUELIN SR TABLETS**
2.00 mm Helvetica Bold Condensed 6.5 pt — **COMPOSITION**

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