# Professional Information

**SCHEDULING STATUS**

**S2**

**1 NAME OF THE MEDICINE**
**Nuelin Liquid**, theophylline 25 mg/5 ml, liquid.

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each 5,0 ml contains:
Theophylline 25,0 mg
Preservatives:
Methyl hydroxybenzoate 0,2 %
Propyl hydroxybenzoate 0,03 %
Contains sugar: Sucrose 2,5 g/5 ml
For full list of excipients see section 6.1.

**3 PHARMACEUTICAL FORM**
**Nuelin Liquid** is a clear, colourless to almost colourless, syrupy liquid with a characteristic odour.

**4 CLINICAL PARTICULARS**
**4.1 Therapeutic indication**
**Nuelin Liquid** is indicated for maintenance treatment of bronchospasm in asthmatic children.
**4.2 Posology and method of administration**
2-8 years:
24 mg / kg per 24 hours, given in 4 divided doses, i.e. every 6 hours
9-12 years:
20 mg / kg per 24 hours, given in 4 divided doses, i.e. every 6 hours
13-16 years:
18 mg / kg per 24 hours, given in 4 divided doses, i.e. every 6 hours
**4.3 Contraindications**
Hypersensitivity to theophylline, xanthine derivatives or any of the excipients included in **Nuelin Liquid**. See 6.1.
Recent myocardial infarction. Acute tachyarrhythmia.
Porphyria.
Concomitant use with ephedrine in children.
**4.4 Special warnings and precautions for use**
Theophylline should not be administered to children younger than two years of age, as they cannot metabolize theophylline sufficiently.
After taking **Nuelin Liquid**, patients should carefully rinse out their mouths with plenty of water. **Nuelin Liquid** is unsuitable for children suffering from diabetes mellitus.
The patient's response to therapy should be carefully monitored.
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 4.5)
Xanthine containing beverages (e,g: tea, coffee, 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).
**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.
Contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take **Nuelin Liquid.**
Contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.
**4.5 Interactions with other medicines and other forms of interaction**
The use of sympathomimetic aerosols should be avoided in patients being treated with **Nuelin Liquid**, as this could lead to an increase in side effects.
The following medicines 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, thiabendazole, disulfiram, Interferon alpha, verapamil, fluvoxamine, tiabendazole, viloxazine.
The following medicines have been shown to increase the hepatic clearance of theophylline, thus lowering its serum concentration:
tobacco or marijuana smoking, phenobarbitone, phenytoin, carbamazepine, ritonavir, rifampicin, sulfinpyrazone. 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 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.
**4.6 Fertility, pregnancy and lactation**
**Women of childbearing potential**

There are no clinical data on fertility in humans. Nonclinical data on theophylline reveal adverse effects on male and female fertility.

**Pregnancy**

Safety in pregnancy has not been established. Theophylline crosses the placental barrier. The effect on foetal development is not known. In premature infants theophylline clearance is significantly decreased. Therefore, if **Nuelin Liquid** is administered to the mother near the time of delivery, the neonate should be monitored closely for the pharmacological effects of theophylline.

**Breastfeeding**

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

**Fertility**

No data available.

**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.

It is not always possible to predict to what extent **Nuelin Liquid** may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which **Nuelin Liquid** affects them.

**4.8 Undesirable effects**

Metabolism and nutrition disorders:

Frequency unknown: Hyperglycaemia, hypokalaemia, hypomagnesaemia.

Psychiatric disorders:

Frequent: Insomnia, anxiety, irritability, agitation, restlessness.

Nervous system disorders:

Frequent: Headache, CNS stimulation reflex hyperexcitability, tremor, convulsion, insomnia.

Cardiac disorders:

Frequent: Tachycardia, palpitations, arrhythmia.

Less frequent: More serious signs of high serum levels (usually above 30 µg/ml), such as cardiac dysrhythmias may appear without prior warning.

Frequency unknown: Extrasystoles.

Vascular disorders:

Frequency unknown: Flushing, hypotension.

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: Tachypnoea.

Gastrointestinal disorders:

Frequent: Gastric irritation, nausea, vomiting, epigastric pain, reactivation of peptic ulcer, gastro-oesophageal reflux, haematemesis.

Frequency unknown: Diarrhoea.

Skin and subcutaneous tissue disorders:

Frequency unknown: Rash, alopecia.

Renal and urinary disorders:

Frequency unknown: Potentiation of diuresis, albuminuria, haematuria, inappropriate ADH secretion (high dose).

Side effects are related to theophylline plasma levels: nausea and vomiting, excitation, nervousness and insomnia occur at plasma concentrations of 20 to 30 mg / L, hysteria at 30 mg / L, cardiac dysrhythmias and coma at concentrations greater than 40 mg / L. These toxic phenomena are enhanced by hypoxia and acidosis. The treatment of toxic effects is symptomatic: (whether or not temporary) discontinuance of the administration of theophylline, correction of the acidosis and hypoxia, and careful supervision of any therapeutic intervention that may aggravate underlying heart or lung diseases, such as overloading with water and salt, oxygen, sedatives, anti-emetics and beta blockers.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8publications: Alternately you can contact iNova Pharmaceuticals (Pty) Ltd at +27 11 087 0000.

Website: www.inovapharma.co.za.

**4.9 Overdose**

**Symptoms:**

Characterized by nausea, vomiting and gastro-intestinal irritation. Tachycardia and hypotension may occur. 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, convulsions, hyperglycaemia, hypomagnesaemia, metabolic acidosis, rhabdomyolysis. 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:

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.

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 4.4)

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.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

A 10.2 Bronchodilators.

Theophylline is a methylated xanthine and is therefore related to caffeine and theobromine. The pharmacological action of theophylline results in the relaxation of smooth muscle.

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.

### 5.2 Pharmacokinetic properties

**Absorption**

Theophylline is well absorbed throughout the gastrointestinal tract.

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

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 4.5) 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.

Not applicable.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

- Berry citrus blend PFC
- Purified water
- Sorbitol 70 % solution
- Sucrose

### 6.2 Incompatibilities

None known.

### 6.3 Shelf life

24 months.

### 6.4 Special precautions for storage

Store at or below 25 °C, protect from light.

KEEP OUT OF REACH OF CHILDREN

### 6.5 Nature and contents of container

**Nuelin Liquid** is available in amber plastic (PET) bottles containing 200 mℓ and 500 mℓ.

### 6.6 Special precautions for disposal

No special requirements.

## 7 HOLDER OF CERTIFICATE OR REGISTRATION

iNova Pharmaceuticals (Pty) Ltd.
15 e Riley Road
Bedfordview
2007

## 8 REGISTRATION NUMBER

S/10.2/126

## 9 DATE OF FIRST REGISTRATION

22 September 1986

## 10 DATE OF REVISION OF THE TEXT

21 May 2021

**ZIMBABWE**
Prescription Preparation (PP10)
22.1.1 Systemic bronchodilators
Reg. No.: 98/22/1.1/3446

**NAMIBIA**
Scheduling status: NS1
Registration no.: 04/10.2/0957