NEW ZEALAND DATA SHEET
NUELIN™ SYRUP

1 PRODUCT NAME
NUELIN 80 mg/15 mL Syrup

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Theophylline BP 80 mg/15 mL

Excipients with known effects:

Methy lhydroxybenzoate
Propyl hydroxybenzoate

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM
Syrup

A clear, almost colourless liquid with a pleasant odour. Each 25mL unit dose contains Theophylline BP 133.3mg in a fruit flavoured aqueous vehicle.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
NUELIN syrup is 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.

Adults
25mL every six hours.

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

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

Children over 2 years: 1mL/kg bodyweight (up to a maximum of 25mL) every six hours.

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

4.3 Contraindications
Hypersensitivity to the active ingredient or excipients listed in section 5.1 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.

Theophyliine 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

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category A

Although theophylline has a Category A rating, it does cross the placental barrier. The effect of 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.

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

NUELIN 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 30µg/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:

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 of 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 1g/kg every 4-6 hours (or 10g/hour) until the theophylline level has plateaued or commenced falling or is below 55µmol/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

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

Absorption

Theophylline is well absorbed throughout the gastrointestinal tract. Peak plasma theophylline levels occur 1½ 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 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 *Interactions*). 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

Berry flavour (mix) F-9756
Methyl hydroxybenzoate
Propyl hydroxybenzoate
Purified water
Sorbitol
Sucrose

6.2 Incompatibilities
None known.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store at or below 30^0C. Keep container tightly closed.

6.5 Nature and contents of container
Bottle, plastic, amber PET with polypropylene child resistant, tamper evident cap: 500 mL

6.6 Special precautions for disposal
No special requirements for disposal.

7 MEDICINE SCHEDULE
Pharmacist only

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
8 November 1977

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 Laboratory test interactions. Section 5.1: Added - Pharmacotherapeutic group: drugs for obstructive airway disease. ATC code: R03DA04. Section 6.1 List of excipients expanded to include all excipients as per TPDR Section 6.5: bottle container material specified

	as per TPDR. Section 8: Sponsor name address changed.