1. NAME OF THE MEDICINAL PRODUCT
   Nuclin SA 250 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
   Theophylline 250mg

   Excipients with known effect:
   Each tablet contains Lactose Ph Eur.

   For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM
   Prolonged release tablet

   The tablets are white, round, biconvex, uncoated tablets with “T” on one face and “250” on the other with a score line

   The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS
   4.1 Therapeutic indications

   Nuclin SA are indicated for the prophylaxis and treatment of reversible bronchospasm associated with asthma and chronic obstructive pulmonary disease.

   Because effective plasma levels are maintained for up to twelve hours from a single dose, less frequent dosing is required than with conventional theophylline preparations.

   Theophylline should not be used as first drug of choice in the treatment of asthma in children.
4.2 Posology and method of administration

Posology

One tablet twice daily, preferably after food, increasing to two tablets twice daily, if necessary.

Paediatric population

Below 6 months: Nuelin should not be used in children below 6 months of age.
Below 6 years: Nuelin should not be used in children below 6 years of age. Other dosage forms are available that are more suitable for children aged less than 6 years.

6 to 12 years: One tablet twice daily, preferably after food.

Elderly

Elderly patients may require lower doses due to reduced theophylline clearance.

Method of administration

Nuelin SA-250 tablets are scored and may be halved but should not be crushed or chewed.

The dosage should be titrated for each individual and adjusted with caution. Serum theophylline levels should be monitored to ensure that they remain within the therapeutic range.

4.3 Contraindications

Porphyria Hypersensitivity to any constituent or to xanthines. Concomitant use with ephedrine in children.

Children under 6 months of age.

Hypersensitivity to the active ingredient or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

The patients response to therapy should be carefully monitored. Worsening of asthma symptoms requires urgent medical attention.

In case of insufficient effect of the recommended dose and in case of adverse events, theophylline plasma concentration should be monitored.

Use with caution in patients with cardiac arrhythmias, peptic ulcer, hyperthyroidism, severe hypertension, acute porphyria, hepatic dysfunction, chronic alcoholism, and chronic lung disease.
Use with caution in patients with acute febrile illness, as fever decreases the clearance of theophylline. It may be necessary to decrease the dose to avoid intoxication.

Smoking and alcohol consumption may increase theophylline clearance and increased doses of theophylline are therefore required. In patients with cardiac failure, hepatic dysfunction/disease and fever the reverse is true and these patients may require a reduced dosage.

Alternative bronchodilator therapy should be used in patients with a history of seizures.

It is not recommended that the product be used concurrently with other preparations containing xanthine derivatives.

WARNINGS: Xanthines can potentiate hypokalaemia resulting from beta-2-agonist therapy steroids, diuretics and hypoxia. Particular caution is advised in severe asthma. It is recommended that serum potassium levels are monitored in such situations.

PRECAUTIONS: In the case of an acute asthmatic attack in a patient receiving a sustained action theophylline preparation, great caution should be taken when administering intravenous aminophylline. Half the recommended loading dose of aminophylline (generally 6 mg/kg) should be given, i.e. 3 mg/kg, cautiously.

4.5 Interaction with other medicinal products and other forms of interaction

Cimetidine, allopurinol, corticosteroids, frusemide, isoprenaline, oral contraceptives, thiobendazole, ciprofloxacin, erythromycin or other macrolide antibiotics and the calcium channel blockers, diltiazem and verapamil, nizatidine, norfloxacin, isoniazid, fluconazole, carbimazole, mexiletine, propafenone, oxpentifylline, disulfiram, viloxazine, interferon alfa, and influenza vaccine increase plasma theophylline concentrations. A reduction of the theophylline dosage is recommended.

Phenytoin, carbamazepine, barbiturates, rifampicin, sulphipyrazone, ritonavir, primidone and aminoglutethimide may reduce plasma theophylline concentrations and therefore the theophylline dosage may need to be increased.

Theophylline can increase lithium excretion.

The concomitant use of theophylline and fluvoxamine should usually be avoided. Where this is not possible, patients should have their theophylline dose halved and plasma theophylline should be monitored closely.

Warnings about the concurrent use of xanthines and xanthine derivatives are shown in Section 4, Special Warnings.
Plasma concentrations of theophylline can be reduced by concomitant use of the herbal remedy St John’s wort (Hypericum perforatum).

Other interactions:
- β-Blockers: antagonism of bronchodilation.
- Ketamine: reduced convulsive threshold.
- Doxapram: increased CNS stimulation.

Also see Warnings.

4.6 Fertility, pregnancy and lactation

Pregnancy
Administration of theophylline drugs during pregnancy should only be considered if there is no safe alternative and the benefits of treatment outweigh the risks.

Breast-feeding
Theophylline is excreted in breast milk and should not therefore be routinely administered to nursing mothers.

4.7 Effects on ability to drive and use machines
Nuelin SA 250mg tablets has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
The side-effects commonly associated with xanthine derivatives such as nausea, gastric irritation, palpitations, tachycardia, arrhythmias, convulsions, headache, CNS stimulation and insomnia are much diminished when a sustained action preparation such as Nuelin SA is used. These side-effects are mild and infrequent when the plasma concentration is maintained at less than 20 microgrammes/ml.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at:
www.mhra.gov.uk/yellowcard

4.9 Overdose
Over 3 g could be serious in an adult (40 mg/kg in a child). The fatal dose may be as
little as 4.5 g in an adult (60 mg/kg in a child), but is generally higher.

**Symptoms**

Warning: Serious features may develop as long as 12 hours after overdosage with sustained release formulations.

**Alimentary features:**
Nausea, vomiting (which is often severe), epigastric pain and haematemesis. Consider pancreatitis if abdominal pain persists.

**Neurological features:**
Restlessness, hypertonia, exaggerated limb reflexes and convulsions. Coma may develop in very severe cases.

**Cardiovascular features:**
Sinus tachycardia is common. Ectopic beats and supraventricular and ventricular tachycardia may follow.

**Metabolic features:**
Hypokalaemia due to shift of potassium from plasma into cells is common, can develop rapidly and may be severe. Hyperglycaemia, hypomagnesaemia and metabolic acidosis may also occur. Rhabdomyolysis may also occur.

**Management**

Activated charcoal or gastric lavage should be considered if a significant overdose has been ingested within 1-2 hours. Repeated doses of activated charcoal given by mouth can enhance theophylline elimination. Measure the plasma potassium concentration urgently, repeat frequently and correct hypokalaemia. BEWARE! If large amounts of potassium have been given, serious hyperkalaemia may develop during recovery. If plasma potassium is low then the plasma magnesium concentration should be measured as soon as possible.

In the treatment of ventricular arrhythmias, proconvulsant antiarrhythmic agents such as lignocaine (lidocaine) should be avoided because of the risk of causing or exacerbating seizures.

Measure the plasma theophylline concentration regularly when severe poisoning is suspected, until concentrations are falling. Vomiting should be treated with an antiemetic such as metoclopramide or ondansetron. Tachycardia with an adequate cardiac output is best left untreated. Beta-blockers may be given in extreme cases but not if the patient is asthmatic.

Control isolated convulsions with intravenous diazepam. Exclude hypokalaemia as a cause.

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5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Pharmacotherapeutic group: drugs for obstructive airway disease, ATC code:
Theophylline directly relaxes smooth muscle thus acting mainly as a bronchodilator and vasodilator. The drug also possesses other action typical of the xanthines derivatives - coronary vasodilator, diuretic, cardiac stimulant, cerebral stimulant and skeletal muscle stimulant.

5.2 Pharmacokinetic properties

It has been established that the xanthines, which include theophylline, are readily absorbed after oral, rectal or parenteral administration and this is well documented in published literature.

Effective plasma concentrations: 5-12 µg/ml (do not exceed 20 µg/ml). Theophylline is mainly excreted by the kidneys.

Theophylline is excreted in the urine as metabolites, mainly 1,3-dimethyluric acid and 3-methylxanthine, and about 10% is excreted unchanged.

Plasma half-lives ranging from 3 to 9 hours and therapeutic plasma concentrations from about 5 to 20 µg per ml have been reported.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Ph Eur
Cellulose Acetate Phthalate Ph Eur
Magnesium Stearate Ph Eur

6.2 Incompatibilities

None known
6.3 **Shelf life**
30 months

6.4 **Special precautions for storage**
Do not store above 25°C

6.5 **Nature and contents of container**
Bottle or Blister packs of 60
Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements for disposal.

7. **MARKETING AUTHORISATION HOLDER**
Meda Pharmaceuticals Ltd
Skyway House
Parsonage Road
Takeley
Bishop’s Stortford
CM22 6PU

8. **MARKETING AUTHORISATION NUMBER(S)**
PL 15142/0114

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
Date of first authorisation: 22 January 1980
Date of latest renewal: 21 August 2004

10. **DATE OF REVISION OF THE TEXT**
23/01/2017