IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0087/002/006
Case No: 2044497

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Rona Laboratories Limited

Harrier House, **High Street**, **West Drayton**, **Middlesex UB7 7QG**, **England**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Slo-Phyllin 250mg Capsules.

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **19/10/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Slo-Phyllin 250mg Capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Theophylline (Anhydrous) Ph. Eur. 250mg.

3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard (blue capsule filled with small white pellets).

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As a bronchodilator in the symptomatic and prophylactic treatment of asthma and for reversible bronchoconstriction associated with chronic bronchitis and bronchial asthma.

4.2 Posology and method of administration

Method of administration: Oral

Dosage

Children:	2 - 6 years (10 - 20kg):	60 - 120mg twice daily
	7 - 12 years (20 - 35kg):	125 - 250mg twice daily
	over 12 years:	250-500 mg twice daily
Adults:		250-500 mg twice daily
Elderly:		There is a tendency for theophylline clearance to decrease with age leading to higher serum levels. A reduction of the adult dosage may therefore be necessary and close monitoring is advised.

Each patient should be titrated to a suitable dosage regimen by clinical assessment. It may also be necessary to measure plasma theophylline levels. Initially the lowest dosage for each group is recommended. This may be increased gradually if optimal bronchodilator effects are not achieved. The total dosage should not normally exceed 24 mg/kg body weight for children and 13 mg/kg for adults. However the plasma theophylline level measured 4-8 hours after dosing and at least three days after any dosage adjustment provides a more accurate assessment of the patients dosage need, especially as significant variations in the rate of drug elimination can occur between individuals. The following table provides a guide:

Plasma level (mcg/ml)	Result	Directions (if clinically indicated)
Below 10	Too low	Increase dose by 25%
10-20	Correct	Maintain dose
20-25	Too high	Decrease dose by 10%
25-30	Too high	Miss next dose and decrease subsequent doses by 25%
Over 30	Too high	Miss next two doses and decrease subsequent doses by 50%

It is advisable to recheck the plasma level after dose adjustment and every 6-12 months.

It is not possible to ensure bioequivalence between different sustained release theophylline products. Once titrated to an effective dose, patients should not be changed from Slo-Phyllin to another prolonged release xanthine preparation without re-titration and clinical assessment.

4.3 Contraindications

Hypersensitivity to theophylline or other xanthines. Concomitant use of theophylline and ephedrine.

4.4 Special warnings and precautions for use

Caution should be exercised in its use in patients with cardiac disease. Severe side effects (cramps, convulsions, supraventricular tachycardia) may appear at very high serum concentrations, in which case medication should be discontinued.

Care should be taken in its use in patients suffering from insomnia.

4.5 Interaction with other medicinal products and other forms of interaction

Care should be taken in its concomitant use with β-adrenergic agonists, glucagon and other xanthine drugs, as these will potentiate the effects of theophylline.

Increased theophylline plasma levels have been described when erythromycin, cimetidine, thiabendazole, hydrocortisone, methyl prednisolone, allopurinol or oral contraceptives are administered concurrently.

Decreased clearance of theophylline may also be associated with influenza immunisation.

Decreased plasma levels of theophylline have been reported with concurrent use of rifampicin, sulphinpyrazone and carbamazepine. Phenytoin has been reported to accelerate the rate of theophylline clearance and theophylline to decrease steady state phenytoin levels.

4.6 Pregnancy and lactation

Not recommended in pregnancy since theophylline is known to cross the placenta and its effects on the foetus have not been established.

Theophylline is excreted in breast milk and therefore should not be used in nursing mothers.

4.7 Effects on ability to drive and use machines

Not known.

4.8 Undesirable effects

Side effects usually occur when theophylline blood levels exceed 20 micrograms/ml and the most common are gastrointestinal disturbances (nausea, vomiting, anorexia). In most cases monitoring of serum theophylline and dose adjustment to achieve 10-20 micrograms/ml will alleviate these side effects.

4.9 Overdose

Signs and symptoms: Headache, nausea, vomiting, restlessness, hypotension, tachycardia, arrhythmias (usually supraventricular tachyarrhythmias), hypokalaemia, CNS depression, convulsions, dehydration and coma may occur. Massive overdosage may result in cardiac inhibition, circulatory and respiratory failure.

Treatment: The stomach should be emptied by gastric lavage and emesis. Repeated doses of activated charcoal should be considered. Blood glucose, electrolytes, arterial gases and pH should be monitored. Serum theophylline should be measured 4 hours after ingestion and at 4 to 12 hourly intervals thereafter if symptoms are severe. Intensive supportive therapy may be required to maintain respiration and cardiovascular function. Convulsions may be controlled by diazepam. Haemoperfusion may be necessary. Slo-Phyllin is a prolonged-release capsule and effects may be slow in onset and prolonged.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The mechanism of action of theophylline is unclear although a number of pharmacological actions have been implicated. The principal of these are:-

1) Inhibition of the enzyme phosphodiesterase leading to raised cyclic AMP levels.

2) Antagonism of adenosine receptors.

3) Inhibition of the intracellular release of calcium.

4) Stimulation of catecholamine release.

5) Anti-inflammatory action possibly involving the inhibition of submucosal oedema.

5.2 Pharmacokinetic properties

Following administration of Slo-Phyllin capsules at an appropriate twice daily dosage, peak levels of theophylline occur 4-8 hours after dosing, and steady state is achieved in 3 days.

Serum half-life is approximately 12 hours. Theophylline and metabolites are excreted mainly by the liver.

5.3 Preclinical safety data

No adverse effects can be predicted from animal toxicology studies other than those documented from human use of theophylline.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Maize Starch
Refined Bleached Shellac
Talc

Capsule shell
Gelatin
Titanium Dioxide (E171)
Erythrosine (E127)
Indigo Carmine (E132)
Black Iron Oxide (E172)

Printing ink
Black iron oxide (E172)
Shellac glaze
Propylene glycol

6.2 Incompatibilities

None stated.

6.3 Shelf Life

Three years.

6.4 Special precautions for storage

Store in a dry place below 25°C.

6.5 Nature and contents of container

Plastic container of 100 capsules. The container is constructed of polypropylene homopolymer with a low density polyethylene cap.

Clear PVC, 250 µm/Aluminium foil, 20 µm, blister packs containing 56 capsules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

None

7 MARKETING AUTHORISATION HOLDER

Rona Laboratories Limited
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England

8 MARKETING AUTHORISATION NUMBER

PA 87/2/6

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2 December 1997.

Date of last renewal: 2 December 2007.

10 DATE OF REVISION OF THE TEXT

October 2009