IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0970/016/001
Case No: 2055856

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

AstraZeneca UK Limited

600 Capability Green, **Luton**, **LU1 3LU**, **United Kingdom**

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

Paludrine Tablets 100mg

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 **20/10/2008**.

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

Paludrine Tablets 100mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg proguanil hydrochloride.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets
White biconvex tablets, plain one side and bisected on the other side with a letter P in each segment.
The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

'Paludrine' is an effective anti-malarial agent. It is indicated for the prevention and suppression of malaria.

4.2 Posology and method of administration

In any locality where drug-resistant malaria is known or suspected it is essential to take local advice on what prophylactic regimen is appropriate. Prophylactic use of 'Paludrine' alone may not be sufficient.

Adults (including the elderly):	Two tablets	(200 mg) daily.
Children:		
Under 1 year:	¼ tablet	(25 mg) daily
1-4 years:	½ tablet	(50 mg) daily
5-8 years:	1 tablet	(100 mg) daily
9-14 years:	1½ tablets	(150 mg) daily
Over 14 years:	Adult dose daily	

Renal Impairment
Based on a theoretical model derived from a single dose pharmacokinetic study, the following guidance is given for adults with renal impairment.

Creatinine clearance ml/min/1.73 m^2	Dosage
≥ 60	200 mg once daily (standard dose)
20 - 59	100 mg once daily
10 - 19	50 mg every second day
< 10	50 mg once weekly

The grade of renal impairment and/or the serum creatinine concentration may be approximately equated to creatinine clearance levels as indicated below.

Creatinine clearance ml/min/1.73 m^2	Approx* Serum creatinine (µmols/L)	Renal Impairment Grade (arbitrarily divided for dosage purposes)
≥60	-	-
20-59	150-300	Mild
10-19	300-700	Moderate
<10	>700	Severe

*Serum creatinine concentration is only an approximate guide to renal function unless corrected for age, weight and sex.

The daily dose is best taken with water, after food, at the same time each day. For a young child, the dose may be administered crushed and mixed with milk, honey or jam.

Non-immune subjects entering a malarious region are advised to begin treatment with ‘Paludrine’ at least 2 days before entering a malarious area. The daily dose of ‘Paludrine’ should be continued throughout exposure to risk and for four weeks after leaving the area.

The value of malaria prophylaxis in subjects with partial immunity is debatable. However, malaria prophylaxis may be of value in certain high risk groups.

4.3 Contraindications

Known hypersensitivity to proguanil hydrochloride or to any of the excipients.

4.4 Special warnings and precautions for use

‘Paludrine’ should be used with caution in patients with severe renal impairment (Section 4.2 Dosage and Method of Administration).

There have been reports of haemotological changes in such patients (section 4.8).

Concomitant administration of magnesium trisilicate with Paludrine is not recommended (section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

A study to evaluate the effect of magnesium trisilicate on the bioavailability of proguanil indicated that proguanil absorption was markedly reduced. The Area Under the Curve (AUC) for proguanil was reduced from 3256 ng.h per ml (proguanil alone) to 1148 ng.h per ml (proguanil/antacid combination). Therefore the concomitant administration of magnesium trisilicate with ‘Paludrine’ is not recommended (section 4.4).

Proguanil can potentiate the anticoagulant effect of warfarin and related anticoagulants through a possible interference with their metabolic pathways. Caution is advised when initiating or withdrawing malaria prophylaxis with Paludrine in patients on continuous treatment with anticoagulants.

4.6 Pregnancy and lactation

Pregnancy: Malaria in pregnant women increases the risk of maternal death, miscarriage, still-birth and low birth weight with the associated risk of neonatal death. Malarial prophylaxis is therefore strongly advised in pregnant women at risk of catching malaria. It is therefore acceptable to take the recommended dosage of Paludrine during all stages of pregnancy. Medical advice should be sought by subjects during the first trimester. Paludrine has been widely used for more than 40 years and a causal connection between its use and any adverse effect on mother or foetus has not been

established.

Lactation: Although Paludrine is excreted in breast milk, the amount is insufficient to confer any benefit on the infant. Separate chemoprophylaxis for the infant is required.

4.7 Effects on ability to drive and use machines

There is no evidence to suggest that 'Paludrine' causes sedation or is likely to affect concentration.

4.8 Undesirable effects

At normal dosage levels the side effect most commonly encountered is mild gastric intolerance, including diarrhoea and constipation. This usually subsides as treatment is continued.

Mouth ulceration and stomatitis have, on occasion, been reported. Isolated causes of skin reactions and reversible hair loss have been reported in association with the use of proguanil.

Rarely, allergic reactions which manifest as urticaria or angioedema and very rarely vasculitis have been reported.

Drug fever and cholestasis may very rarely occur in patients receiving Paludrine.

Haematological changes in patients with severe renal impairment have been reported.

The following effects have been reported in cases of overdosage: haematuria, renal irritation, epigastric discomfort and vomiting.

4.9 Overdose

There is no specific antidote and symptoms should be treated as they arise.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarials
ATC code: P01B B01
'Paludrine' is effective against the tissue forms of some strains of *P.falciparum* and acts through an active metabolite cycloguanil. The mechanism of action is probably due to inhibition of dihydrofolate reductase. The effect of this action is to prevent schizogany and its main effect is against the developing primary tissue schizonts.

5.2 Pharmacokinetic properties

Absorption: Rapid, reaching a peak at 3 to 4 hours. The active metabolite (cycloguanil) peaks somewhat later (4 to 9 hours).

Half-life: The half-life of proguanil is 14-20 hours whilst cycloguanil has a half-life of the order of 20 hours. Accumulation during repeated dosing is therefore limited, steady-state being reached within approximately 3 days.

Metabolism: Transformation of proguanil into cycloguanil is associated with cytochrome P450, CYP 2C19, activity. A smaller part of the transformation of proguanil into cycloguanil is probably catalysed by CYP 3A4.

Elimination: Elimination occurs both in the faeces and, principally, in the urine.

In the event of a daily dose being missed, the blood levels fall rapidly but total disappearance of the drug only occurs 3 to 5 days after stopping treatment.

5.3 Preclinical safety data

Proguanil is a drug on which extensive clinical experience has been obtained. All relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium carbonate
Gelatin
Magnesium stearate
Maize starch

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

HDPE bottle containing 100 tablets.

PVC/PVDC and aluminium backed blisters in packs of 98 tablets.

Not all pack sizes may be marketed.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited
600 Capability Green
Luton
Bedfordshire LU1 3LU
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 970/16/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1977

Date of last renewal: 01 April 2007

10 DATE OF REVISION OF THE TEXT

September 2008