Pharmaceutical form
White, bi-convex tablets plain on one side and bisected on the other side with a letter P in each segment. Each tablet contains 100 mg of Proguanil Hydrochloride BP. Inactive ingredients are calcium carbonate, gelatin, magnesium stearate and maize starch.

Therapeutic Indication
‘Paludrine’ is an effective antimalarial agent. It is recommended for the prevention and suppression of malaria.

Posology and method of administration
Non-immune subjects entering a malarious area are advised to begin treatment with ‘Paludrine’ 1 week before, or if this is not possible then at least 2 days before entering the malarious area. The daily dose of ‘Paludrine’ should be continued throughout exposure to risk and for 4 weeks after leaving the area.

Adults:
2 tablets (200 mg) daily.

Children
Under 1 year: 1/4 tablet (25 mg) daily.
1-4 years: 1/2 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.
The daily dose is best taken with water, after food, at the same time each day.
Provided the tablet fragment gives the minimum amount specified, precise accuracy in children’s dosage is not essential since the drug possesses a wide safety margin.
For a young child, the dose may be administered crushed and mixed with milk, honey or jam. The treatment should be started at least two days before entering the malarious area and continued for the whole period of stay and four weeks after leaving the area.
Elderly patients: There are no special dosage recommendations for the elderly, but it may be advisable to monitor elderly patients so that optimum dosage can be individually determined.
Renal impairment: Based on a theoretical model derived from a single dose pharmacokinetic study the following guidance is given for adults with renal impairment. See also “Special Warnings and Precautions for Use”.

<table>
<thead>
<tr>
<th>Creatinine clearance ml/min/1.73 m²</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>200 mg once daily (standard dose)</td>
</tr>
<tr>
<td>20 -59</td>
<td>100 mg once daily</td>
</tr>
<tr>
<td>10 - 19</td>
<td>50 mg every second day</td>
</tr>
<tr>
<td>&lt;10</td>
<td>50 mg once weekly</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Creatinine clearance ml/min/1.73 m²</th>
<th>Approx* Serum creatinine (micromol/l)</th>
<th>Renal Impairment Grade (arbitrarily divided for dosage purposes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20 to 59</td>
<td>150 to 300</td>
<td>Mild</td>
</tr>
<tr>
<td>10 to 19</td>
<td>300 to 700</td>
<td>Moderate</td>
</tr>
<tr>
<td>&lt;10</td>
<td>&gt;700</td>
<td>Severe</td>
</tr>
</tbody>
</table>

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

Contraindications
‘Paludrine’ should be used with caution in patients with severe renal impairment.
(see Posology and method of administration and Special warnings and precautions for use).

Special warnings and precautions for use
‘Paludrine’ should be used with caution in patients with severe renal impairment (see Posology and method of administration). There have been rare reports of haematological changes in such patients. In any locality where drug resistant malaria is known or suspected, it is essential to take local medical advice on what prophylactic regimen is appropriate. Prophylactic use of ‘Paludrine’ alone may not be sufficient.
Interactions
Antacids may reduce the absorption of proguanil, so should be taken at least 2-3 hours apart.

Pregnancy and Lactation
Pregnancy: ‘Paludrine’ has been widely used for over 40 years and a causal connection between its use and any adverse effect on mother or foetus has not been established.

However, Paludrine should not be used during pregnancy unless, in the judgement of the physician, potential benefit outweighs the risk.

Malaria in pregnant women increases the risk of maternal death, miscarriage, still-birth and low birth weight with the associated risk of neonatal death. Although travel to malarious areas should be avoided during pregnancy, if this is unavoidable effective prophylaxis is therefore strongly advised in pregnant women.

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.

Effect on ability to drive and use machines
There is no evidence to suggest that ‘Paludrine’ causes sedation or is likely to affect concentration.

Undesirable effects
At normal dosage levels the side effect most commonly encountered is mild gastric intolerance. This usually subsides as treatment is continued.

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

Rarely, allergic reactions, which manifest as urticaria or angioedema have been reported.

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

Overdose
The following effects have been reported in cases of overdosage: haematuria, renal irritation, epigastric discomfort and vomiting. There is no specific antidote and symptoms should be treated as they arise.

Pharmacological properties
Pharmacodynamic properties
‘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 schizogony and its main effect is against the developing primary tissue schizonts.

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 to 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 fail rapidly but total disappearance of the drug only occurs 3 to 5 days after stopping treatment.

Special precautions for storage
Do not store above 30oC

Shelf life
Please refer to expiry date on the blister strip or outer carton.

Pack Size
Please refer to the outer carton for pack size.

Date of revision of text
25 October 2001