



BRAND NAME:	KOYODRINE
GENERIC NAME:	PROGUANIL TABLETS BP 100 MG

1. Name of the Medicinal Product

KOYODRINE

(PROGUANIL TABLETS BP 100 MG)

1.1 (Trade) name of product

KOYODRINE

1.2 Strength

Proguanil Hydrochloride BP 100 mg

1.3 Pharmaceutical Dosage Form

Tablets

2. QUALITATIVE & QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Each Uncoated tablet contains:

Proguanil Hydrochloride BP.....100 mg

Excipientq.s.

	
BRAND NAME:	KOYODRINE
GENERIC NAME:	PROGUANIL TABLETS BP 100 MG

2.2 Quantitative Composition:

Batch Size: 127.04 Kg (1,60,000 Tablets)

Sr. No.	Ingredients	Specification	Unit Formula (mg)	Batch Formula (Kg)
Granulation				
Dry Mixing				
1.	Proguanil Hydrochloride	BP	100.00	10.000*
2.	Maize Starch	BP	42.320	4.655**
3.	Microcrystalline Cellulose	BP	23.000	2.300
4.	Crosspovidone	USP	11.000	1.100
Binder				
5.	PVP K-30	BP	3.500	0.350
6.	Sodium Benzoate	BP	0.180	0.018
7.	Maize Starch	BP	5.000	0.500
8.	Purified Water	BP	q.s	10.00
Lubricants				
7.	Purified Talc	BP	4.000	0.400
8.	Crosspovidone	USP	3.000	0.300
9.	Colloidal Anhydrous Silica	BP	4.000	0.400
10.	Magnesium Stearate	BP	4.000	0.400
Total weight of Tablet			200.00 mg	20.00 kg

Remarks:

* Quantity of Proguanil Hydrochloride is taken after calculation based on assay.

**10 % extra starch added to compensate loss on drying & Maize Starch quantity change according to change in quantity of Proguanil Hydrochloride.

3. PHARMACEUTICAL DOSAGE FORM

Tablets

White round shaped, standard concave uncoated tablet with debossing ‘‘KOYODRINE’’ on one side & ‘‘P breakline P’’ on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Koyodrine Tablets is an effective antimalarial agent. It is recommended for the prevention and suppression of malaria.



BRAND NAME:	KOYODRINE
GENERIC NAME:	PROGUANIL TABLETS BP 100 MG

4.2 Posology and Method of Administration

Oral use

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

Adults:

Two tablets (200 mg) daily.

Paediatric population:

Under 1 year:	1/4 tablet (25 mg) daily
1 to 4 years:	1/2 tablet (50 mg) daily
5 to 8 years:	1 tablet (100 mg) daily
9 to 14 years:	1 1/2 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.

Older people: 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 Sections 4.3 and 4.4)

Creatinine clearance (ml/min 1.73 m²)	Dosage
≥ 60	200 mg once daily (standard dose)
20 to 59	100 mg once daily
10 to 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.



BRAND NAME:	KOYODRINE
GENERIC NAME:	PROGUANIL TABLETS BP 100 MG

Creatinine clearance (ml/min/1.73 m²)	Approx* serum creatinine (micromol/l)	Renal Impairment Grade (arbitrarily divided for dosage purposes)
≥ 60	-	-
20 to 59	150 to 300	Mild
10 to 19	300 to 700	Moderate
< 10	> 700	Severe

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

4.4 Special warnings and special precautions for use

Renal Impairment:

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

Koyodrine should be used with caution in patients with severe renal impairment.

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 Koyodrine alone may not be sufficient.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids

Antacids may reduce the absorption of proguanil, so should be taken at least 2-3 hours apart.

Anticoagulants

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 Koyodrine in patients on continuous treatment with anticoagulants.

Live oral typhoid vaccination (Ty21a strain)

Proguanil should be stopped 3 days before and should not be started until 3 days after receiving live oral typhoid vaccination (Ty21a strain).



BRAND NAME:	KOYODRINE
GENERIC NAME:	PROGUANIL TABLETS BP 100 MG

Boosted protease-inhibitors

When given with boosted protease-inhibitors, reduction in Proguanil exposure has been observed. This combination should be avoided when possible.

4.6 Fertility, Pregnancy and lactation

Pregnancy: There are limited data available from the use of Proguanil in pregnant women.

Koyodrine should not be used during pregnancy unless, in the judgment 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.

Proguanil is a dihydrofolate reductase inhibitor (see section 5.1) and adequate folate supplements should be given to pregnant women taking Proguanil.

Lactation: Although Koyodrine 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 Koyodrine causes sedation or is likely to affect concentration.

4.8 Undesirable effects

Undesirable effects are listed by MedDRA System Organ Classes.

Assessment of undesirable effects is based on the following frequency groupings:

Very common: $\geq 1/10$

Common: $\geq 1/100$ to $<1/10$

Uncommon: $\geq 1/1,000$ to $<1/100$

Rare: $\geq 1/10,000$ to $<1/1,000$

Very rare: $<1/10,000$

Not known: cannot be estimated from the available data

	
BRAND NAME:	KOYODRINE
GENERIC NAME:	PROGUANIL TABLETS BP 100 MG

System Organ Class	Undesirable Effect and Frequency
Blood and lymphatic system disorders	<i>Not known</i> Hematological changes such as aplastic anaemia, anaemia megaloblastic and pancytopenia (see section 4.4)
Immune system disorders	<i>Not known</i> Hypersensitivity, including urticaria, angioedema Vasculitis
Gastrointestinal disorders	<i>Not known</i> Gastric disorder, including diarrhoea and constipation* Mouth ulceration Stomatitis
Hepatobiliary disorders	<i>Not known</i> Cholestasis
Skin and subcutaneous tissue disorders	<i>Not known</i> Skin reactions such as skin exfoliation, rash, pruritus and alopecia**
General disorders and administration site conditions	<i>Not known</i> Pyrexia

* usually subsides as treatment is continued.

**reversible alopecia

4.9 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.

Consider activated charcoal in patients who have ingested 30 mg/kg or more within 1 hour. Check urea and electrolytes (U&Es), liver function test (LFTs) and full blood count (FBC) in all patients. Check FBC again 3 days and again one week after the overdose or in case any new symptoms appear.

5. Pharmacological properties

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Antiprotozoals, Antimalarials, **ATC code:** P01BB01

Proguanil is an antimalarial drug and dihydrofolate reductase inhibitor. It acts like the other antifolate antimalarials by interfering with the folic-folinic acid systems and thus exerts its effect mainly at the time the nucleus is dividing. Since its activity is dependent on its metabolism, Proguanil has a slow schizonticidal effect in the blood. It also has some schizonticidal activity in the tissues.



BRAND NAME:	KOYODRINE
GENERIC NAME:	PROGUANIL TABLETS BP 100 MG

Proguanil is effective against the exoerythrocytic forms of some strains of plasmodium falciparum but it has little or no activity against the exoerythrocytic forms of P. Vivax. It has a marked sporonticidal effect against some strains of p falciparum; it does not kill the gametocytes, but renders them non-infective for the mosquito while the drug is present in the blood. Malaria parasites in the red blood cells are killed more rapidly by chloroquine or quinine than by Proguanil, which is therefore not the best drug to use for the treatment of acute malaria.

Soon after Proguanil was introduced, it was observed that the drug was inactive as an inhibitor of the in vitro growth of P. Gallinaceum and P. Cynomolgi, but that sera from dosed monkeys were active against p. Cynomolgi in vitro. These findings suggested that proguanil was activated in vivo.

Since that time it has been accepted by most investigators in this field that cycloguanil is the active metabolite of proguanil and that parent compound is inactive per se.

Cycloguanil acts by binding to the enzyme dihydrofolate reductase in the malaria parasite. The effect of this action is to prevent the completion of schizogony. This is seen in the asexual blood stages as an arrest of maturation of the developing schizonts and an accumulation of large, abnormal looking trophozoites.

Proguanil is highly active against the primary exoerythrocytic forms of p. Falciparum and it has a fleeting inhibiting action on those of p. Vivax. Proguanil is therefore a valuable drug for causal prophylaxis in falciparum malaria.

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 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.



BRAND NAME:	KOYODRINE
GENERIC NAME:	PROGUANIL TABLETS BP 100 MG

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

Data not available

6. Pharmaceutical Particulars

6.1 List of excipients

Maize Starch, Microcrystalline Cellulose, Crosspovidone, PVP K-30, Sodium Benzoate, Purified Water, Purified Talc, Colloidal Anhydrous Silica & Magnesium Stearate.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C in a dry place, protect from light.

6.5 Nature and contents of container

1x100's tablets in Plastic Bottle.

7. Marketing authorization holder

MAXHEAL LABORATORIES PVT. LTD.

Plot No.-2-7/80-85 Sursez, Sachin,

Dist.: Surat (Gujarat) 394 230



BRAND NAME:	KOYODRINE
GENERIC NAME:	PROGUANIL TABLETS BP 100 MG

8. Marketing authorisation number(s)

Not Applicable.

9. Date of first authorisation/renewal of the authorization

Not Applicable.

10. Date of revision of the text

Not Applicable.