REMAL TABLETS

(Dihydroartemisinin 40MG + Piperaquine Phosphate 320MG)

(For oral use only)

Drug description: REMAL is a compound containing 40mg of dihydroartcmisinin and 320mg of Piperaquine Phosphate and necessary excipients in each tablet

General name: Dihydroartemisinin + Piperaquine Phosphate

Trade name: REMAL

Pharmacological and toxicological actions: The product is a compound antimalarial drug containing dihydroartemisinin and piperaquine. Dyhydroartcmisnin has strong schizontocidal action against plasmodium agamic body, and can destroy plasmodium rapidly, controlling the symptoms immediately.

Pharmacological studies show that the combination of the two products has synergistic effect, and postpone drug resistance of plasmodium. Toxicological studies show that, compared with individual ingredient, theoretical LD_{50} of compound dihydroartemisinin is 806.7 mg/kg, while the test result is 964.26mg/kg, the ratio is 0.84, which is far less than 2.5. the toxicity of RMAL does not increase.

Psychoneurotic system: The doses of 13.36mg/kg (ten times of ED_{90} dose) were used for oral administration. The result showed that REMAL had no abnormal influence on the general behavior of mice according to Irwin's Behavior Grading Method. Cage-shaking test shows that the dose of 13.36mg/kg and 133.60mg/kg of REMAL had no significant influence on the spontaneous activity of mice. Phenobarbital sodium subthreshold hypnotic test showed that REMAL had no significant influence on sleeping rate, sleeping time or sleeping duration of mice, while it tended to prolong the sleeping duration with ten times of ED_{90} dose, which indicates that REMAL may have a certain sedative effect.

Cardiovascular System: The dose of 11.50mg/kg (Monkey curative dose) and 34.50mg/kg (three times of monkey curative dose) were used for oral administration. The result showed that REMAL had no significant influence on heart rate, blood pressure, frequency and depth of breath, P-R QRS, T, ST of ECG

on the anesthetic Beagle dogs on 15, 30, 60, 90,120, 150,180, 210 and 240 minutes after medication.

REMAL has a rapid and powerful plasma schizonticide with rapid symptom control and effectiveness for multi-drug resistant falciparum malaria, and remarkable inhibitory effect on falciparum gametocyte thus minimizing the malaria transmissibility, Pharmacodynamic studies on mice and monkeys demonstrated that two ingredients of REMAL have obvious synergistic effect. In the studies of 975 cases of falciparum malaria and 171 cases of vivax malaria in multi-drug resistant falciparum malaria endemic areas, with follow up for 28 days, the cure rate of falciparum malaria was 96.9% with recrudescence rate of 3.1%; the recurrence rate vivax malaria was 2.7%. The fever clearance time was 16-25 hours and the parasite clearance time was 24-56 hours.

No adverse reactions were found in dogs with 53mg/kg (bas 36.77mg/kg), 80mg/kg (base 55.49mg/kg) and 120mg/kg (base 83.25mg/kg) dose. Bur the dog with 80mg/kg (base 55.49mg/kg) appeared elevation of ALT and CPK.

After administration of drug, the dog with 270mg/kg (base 187.30mg/kg) had vomiting at 2^{nd}, 4^{th} hour, lassitude and anorexia on the 2^{nd}, 3^{rd} day, which returned to normal on the 4^{th} day. No abnormal changes were found except for transient CPK elevation. The dog with 405mg/kg (base 280.9kmg/kg) appeared vomiting once at 2^{nd}, 4^{th} 6^{th} hours respectively, lassitude and anorexia on the 2^{nd}, 3^{rd}, 4^{th} days with transient elevation ALT, AST and CPK after administration. The dog of 607.5mg/kg (base 421.43mg/kg) died at 18^{th} hour after medication.

It presented with incontinence, general tremor, somnolence and exhaustion before death. Its ALT, AST, LDIL, CPK, BUN and CREA elevated obviously. There was shortened Q-T interval at 2^{nd} hour and paroxysmal ventricular tachycardia at 18^{th} hour on ECG after medication. The ALD is 405/kg (base 280.96mg/kg), the MTD is 80mg/kg (base 55.49mg/kg) in a single oral dose of REMAL tablet in beagle dogs

Acute Toxicity: LD_{50} of REMAL in mice was 1390mg/kg (base 964.26mg/kg) by intragastric administration and 582mg/kg (base 403.74mg/kg) by intraperitoncal injection. It showed no significant difference in different sex of mice. The ratio of theoretical value and tested value of LD_{50} of REMAL was 0.84, it indicates that toxicity is additive only.

Chronic Toxicity: 20 (base 13.88) MKD X 4 is a safety dose. 40 (base 27.75) MKD X 4 is a mild-moderate intoxication dose. 80 (base 55.49) MKD X 4 is a severe

intoxication dose. Toxic target organ is mainly the liver. The sensitive index ir reticulocyte. The toxic lesion is reversible. 120 (base 332.98) MKD X 4 is a moderate-severe intoxication dose. Toxic target organ is the liver. The toxic lesion caused by REMAL in rats is reversible.

Pharmacokinetics: After oral administration, REMAL is absorbed by gastrointestinal tract, where dihydroartemisinin is well well absorbed with rapid effect, wide distribution and rapid excretion and metabolism. In 30 minutes after oral administration, piperaquine is detected, Blood peak concentration is reached in 1-2 hours, After absorption, via kidney and intestinal tract. As artemisnin derivatives are antimalarial drug with short half -life and rapid effect, and can kill plasmodium rapidly, in combination with piperaquine that has long half-life. REMAL is effective in inhibiting growth of plasmodium and reducing the relapse rate of malaria.

INDICATION:

REMAL is used in treatment of all kinds of malaria including chloroquine-resistant P.falciparium and P. vivax malaria.

CONTRA-INDICATION:

1. Those who are allergic to any of the two active ingredients are prohibited to use.
2. Those with severe liver or kidney diseases, haematophathy (e.g Leucopenia or thrombocytopenia) porphyria are prohibited to use.

INTERACTION:

Avoid concomitant administration with drugs that may increase the QT interval.

PRECAUTIONS:

1. Those with insufficient liver of kidney functions should take with care.
2. Follow strictly the specified usage and dosage.
3. Contact promptly the doctor when the clinical symptoms are not significantly improved.

USAGE IN PREGNANCY OR LACTATING WOMEN

Pregnancy or lactating patients should take with care when administration is necessary. Doctor’s advice should be followed.

Old aged: Old aged should take with care under monitor of doctors or nurses.

ADVERSE REACTIONS

Rare (<6%), may include:

- Digestive tract: such as nausea, vomiting, impaired appetite, adnominal pain, diarrhea and salivation etc.
- Nerve system: such as dizziness, headache, tinnitus, and asthenia,
- Allergic reaction: Skin itch and eruption etc.
- Laboratory abnormal: transient peripheral erythropenia, transient increase of SGPT and SGOT, leucopenia and thromobocytopenia, and prolongation of QT interval.

OVERDOSAGE AND TREATMENT

In the event of over dosage, activated charcoal should be given if the patient present within 1 hour of ingestion of overdose. Patients should be treated symptomatically and full supportive measures employed.

DOSAGE AND ADMINISTRATION

- Swallow the tablets with a little water, after a meal.
- For young children, tablets can be crushed and given with some water.
- Medicine are given only once a day, a complete treatment is for 3 days

The usual mean dose is

Weight	Age	REMAL Day 1	 Day 2	 Day3
10-20kg	2-7kg	1	1	1
20-40kg	8-13	2	2	2
>40kg	>14yrs	3	3	3

If you take more REMAL than you should have, please consult your doctor or pharmacist

PRESENTATION:

REMAL is available in box of 9 tablets

STORAGE:

Do not store above 30^0c

KEEP OUT OF REACH OF CHILDERN

SHELF VALIDITY – 3 years