ROTRIF®

(Artemether/Lumefantrine)

روٹرِف

Powder for Oral Suspensions, Tablets

DESCRIPTION:

ROTRIF is a fixed dose artemisinin-based combination therapy (ACT) combining artemether, an artemisinin derivative, and lumefantrine, a synthetic antimalarial drug.

QUALITATIVE AND QUANTITATIVE COMPOSITION:

ROTRIF (Artemether/Lumefantrine) is available for oral adminstration as:

1. **ROTRIF 15mg/90mg/5mL Suspension**
   Each reconstituted 5mL contains:
   Artemether.....15mg
   Lumefantrine.....90mg
   (Product Specs.: IP)
2. **ROTRIF DS 30mg/180mg/5mL Suspension**
   Each reconstituted 5mL contains:
   Artemether.....30mg
   Lumefantrine.....180mg
   (Product Specs.: Sigma)
3. **ROTRIF 20mg/120mg Tablet**
   Each dispersible tablet contains:
   Artemether.....20mg
   Lumefantrine.....120mg
   (Product Specs.: IP)
4. **ROTRIF 40mg/240mg Tablet**
   Each tablet contains:
   Artemether.....40mg
   Lumefantrine.....240mg
   (Product Specs.: IP)
5. **ROTRIF 80mg/480mg Tablet**
   Each tablet contains:
   Artemether.....80mg
   Lumefantrine.....480mg
   (Product Specs.: IP)

CLINICAL PHARMACOLOGY:

Mechanism of Action:

The site of antiparasitic action of both components is the food vacuole of the malarial parasite, where they are thought to interfere with the conversion of haem, a toxic intermediate produced during hemoglobin breakdown, to the nontoxic hemozoin, malarial pigment. Both Artemether and Lumefantrine have a secondary action involving inhibition of nucleic acid and protein synthesis within the malarial parasite.

Pharmacokinetics:

Absorption:

Artemether is absorbed fairly rapidly with peak plasma concentrations reaching about 2 hours after dosing. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration about 6-8 hours after dosing. Food enhances the absorption of both Artemether/Lumefantrine.

Distribution:

Artemether and Lumefantrine are both highly bound to human serum proteins in vitro (95.4% and 99.7%, respectively). The artemisinin metabolite dihydroartemisinin is also bound to human serum proteins (47% - 76%).

Metabolism:

Artemether is rapidly and extensively metabolized by CYP3A4/5 to the biologically active metabolite dihydroartemisinin. Lumefantrine is N-butylated, mainly by CYP3A4.

Elimination:

Artemether and dihydroartemisinin are rapidly cleared from plasma with an elimination half-life of 2 hours. Lumefantrine is eliminated very slowly with a terminal half-life of 2-3 days in healthy person and 4-6 days in patients with falciparum malaria.

THERAPEUTIC INDICATIONS:

ROTRIF is indicated for the treatment of uncomplicated infections with *Plasmodium falciparum,* including multidrug resistant strains in adult, children and infants of 5kg and above.

DOSAGE AND ADMINISTRATION:

ROTRIF should be taken with food or milk.

ROTRIF Powder for Oral Suspensions

Once daily at 0, 24, and 48 hours on days 1, 2 and 3							
Body Weight		**5.0 - 7.4 kg**	**7.5 - 9.9 kg**	**10 - 12.4 kg**	**12.5 - 14.9 kg**	**15 - 17.4 kg**	**17.5 - 19.9 kg**
DOSAGE	15mg/90mg/5mL	7mL	10mL	14mL	17mL	20mL	24mL
	30mg/180mg/5mL	3.5mL	5mL	7mL	8.5mL	10mL	12mL

OR as prescribed by the physician.

Directions for Reconstitution:

Fill previously boiled and cooled water upto the mark on the bottle and shake vigorously. Keep the cap tightly closed after use. The reconstituted suspension can be used within 7 days.

ROTRIF 20mg/120mg Tablets

Body Weight (kg)	Each at 0 Hrs (Initial diagnosis), 8 Hrs, 24 Hrs, 36 Hrs, 48 Hrs, 60 Hrs
<5	Not Recommended at this time
5-14	1 Tablet
15-24	2 Tablets
25-34	3 Tablets
> 34	4 Tablets

ROTRIF 40mg/240mg Tablets

Body Weight (kg)	Each at 0 Hrs (Initial diagnosis), 8 Hrs, 24 Hrs, 36 Hrs, 48 Hrs, 60 Hrs
15-24	1 Tablet
25-34	1.5 Tablets
> 34	2 Tablets

ROTRIF 80mg/480mg Tablets

Body Weight (kg)	Each at 0 Hrs (Initial diagnosis), 8 Hrs, 24 Hrs, 36 Hrs, 48 Hrs, 60 Hrs,
> 34	1 Tablet

Patients who vomit within 1 hour of taking the medication should repeat the dose.

CONTRAINDICATIONS:

ROTRIF combination is contraindicated in:

- Patients with known hypersensitivity to the active substances or to any of the excipients.
- Patients who are taking any drug which is metabolized by the cytochrome enzyme CYP2D6.
- Patients with a family history of QTc prolongation interval, or with any other clinical condition or drugs known to prolong the QTc interval.
- Patients with a history of symptomatic cardiac arrhythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
- Patients with disturbances of electrolyte balance e.g. hypokalemia or hypomagnesemia.
- **ROTRIF** should not be administered earlier than one month after the last halofantrine dose.
- **ROTRIF** tablets are not indicated for prophylaxis, or for treating severe malaria, or malaria with pulmonary edema or renal failure. It is also not indicated for and has not been evaluated in the treatment of malaria due to *P. vivax, P. malaria* or *P. ovale.*

PRECAUTIONS:

- **ROTRIF** should not be given concurrently with any other anti-malarial agent unless there is no other treatment option.
- Caution is advised when administering **ROTRIF** to patients with severe renal, hepatic or cardiac problems.
- Caution is recommended when combining **ROTRIF** with drugs exhibiting variable patterns of inhibition, induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered.
- If quinine is given after Artemether/Lumefantrine then close monitoring of ECG is advised, while if **ROTRIF** are given after mefloquinine, then close monitoring of food intake is required.
- The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with **ROTRIF** combination.
- Artemether/Lumefantrine combination has the potential to cause QT prolongation.
- Patients receiving Artemether/Lumefantrine combination should be warned that dizziness or fatigue might occur in which they should not drive or use machines.

Pregnancy:

During the first, second and third trimester, treatment with **ROTRIF** combination should only be considered if the expected benefit to the mother outweighs the risk to the fetus.

Nursing mothers:

Women taking Artemether/Lumefantrine combinations should not breast-feed during their treatment, unless potential benefits to the mother and child outweigh the risks of **ROTRIF** combination treatment.

DRUG INTERACTIONS:

Interaction with other antimalarials:

Mefloquine:

Pre-treatment with mefloquine has no effect on plasma concentrations of artemether but there was a significant reduction in plasma levels of lumefantrine. Patients should be encouraged to eat at dosing times to compensate for the decrease in bioavailability.

Quinine:

Infusion of quinine alone caused a transient prolongation of the QTc interval, which was consistent with its known cardiotoxicity. Thus, prior administration of **ROTRIF** combination appears to enhance the inherent risk of QTc prolongation from IV quinine.

Interaction with CYP450 3A4 inhibitors (Ketoconazole):

The concurrent oral administration of ketoconazole with **ROTRIF** combination led to a modest increase (≤2-fold) in artemether, DHA, and lumefantrine exposure in healthy subjects. Dose adjustment of **ROTRIF** is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

Halofantrine:

In vitro studies indicated that lumefantrine metabolism is inhibited by halofantrine. In patients previously treated with halofantrine, **ROTRIF** combination should be dosed at least one month after the last halofantrine dose.

ADVERSE REACTIONS:

Very Common: Palpitations, headache, dizziness, abdominal pain, anorexia, vomiting, nausea, arthralgia, myalgia, fatigue and sleep disorders.
Common: Amnesia, paraesthesia, diarrhea, pruritus, rash, cough, electrocardiogram QT prolongation, gait disturbances and insomnia.
Uncommon: Liver function test increased, clonus, hypoesthesia, ataxia and somnolence.
Rare: Hypersensitivity.

OVERDOSAGE:

In cases of suspected overdosage symptomatic and supportive therapy should be given as appropriate, which should include ECG and blood potassium monitoring.

INSTRUCTIONS:

- Store below 30°C.
- Protect from light & moisture.
- Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

HOW SUPPLIED:

ROTRIF (Artemether/Lumefantrine) 15mg/90mg/5mL Powder for Oral Suspension is available in pack size of 30 mL & 60mL Bottles.
ROTRIF-DS (Artemether/Lumefantrine) 30mg/180mg/5mL Powder for Oral Suspension is available in pack size of 30 mL & 60mL Bottles.
ROTRIF (Artemether/Lumefantrine) 20mg/120mg Tablets are available in pack of 16's.
ROTRIF (Artemether/Lumefantrine) 40mg/240mg Tablets are available in pack of 10's.
ROTRIF (Artemether/Lumefantrine) 80mg/480mg Tablets are available in pack of 4's & 6's.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات: دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
روشنی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
انتباہ: صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

SIGMA PHARMA

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