

MALARIA, Treatment of (*Plasmodium falciparum*,¹ *P. vivax*,² *P. ovale*, and *P. malariae*³)

	Drug	Adult dosage	Pediatric dosage
ORAL⁴			
<i>P. falciparum</i> or unidentified species acquired in areas of chloroquine-resistant <i>P. falciparum</i>³			
Drug of choice: ⁵	Atovaquone/ proguanil ⁷	2 adult tabs bid ⁶ or 4 adult tabs once/d x 3d	<5kg: not indicated 5-8kg: 2 peds tabs once/d x 3d 9-10kg: 3 peds tabs once/d x 3d 11-20kg: 1 adult tab once/d x 3d 21-30kg: 2 adult tabs once/d x 3d 31-40kg: 3 adult tabs once/d x 3d >40kg: 4 adult tabs once/d x 3d
	OR Quinine sulfate plus doxycycline ^{9,10,11} or plus tetracycline ^{9,10} or plus clindamycin ^{9,12,13} Mefloquine ^{15,16}	650 mg q8h x 3 or 7d ⁸ 100 mg bid x 7d 250 mg qid x 7d 20 mg/kg/d in 3 doses x 7d ¹⁴ 750 mg followed 12 hrs later by 500 mg	30 mg/kg/d in 3 doses x 3 or 7d ⁸ 4 mg/kg/d in 2 doses x 7d 25 mg/kg/d in 4 doses x 7d 20 mg/kg/d in 3 doses x 7d 15 mg/kg followed 12 hrs later by 10 mg/kg
Alternative: ⁵	OR Artemether/ lumefantrine ^{17,18*}	6 doses over 3d (4 tabs/dose at 0, 8, 24, 36, 48 and 60 hours)	6 doses over 3d at same intervals as adults; <15kg: 1 tab/dose 15-25kg: 2 tabs/dose 25-35kg: 3 tabs/dose >35kg: 4 tabs/dose
	OR Artesunate ^{17*} plus see footnote 19	4 mg/kg/d x 3d	4 mg/kg/d x 3d
<i>P. vivax</i> acquired in areas of chloroquine-resistant <i>P. vivax</i>²			
Drug of choice: ⁵	Mefloquine ¹⁵	750 mg PO followed 12 hrs later by 500 mg	15 mg/kg PO followed 12 hrs later by 10 mg/kg
	OR Atovaquone/ proguanil ⁷	2 adult tabs bid ⁶ or 4 adult tabs once/d x 3d	<5kg: not indicated 5-8kg: 2 peds tabs once/d x 3d 9-10kg: 3 peds tabs once/d x 3d 11-20kg: 1 adult tab once/d x 3d 21-30kg: 2 adult tabs once/d x 3d 31-40kg: 3 adult tabs once/d x 3d >40kg: 4 adult tabs once/d x 3d
Alternative: ⁵	either followed by primaquine phosphate ²⁰ Chloroquine phosphate ²¹	30 mg base/d PO x 14d 25 mg base/kg PO in 3 doses over 48 hrs ²²	0.6 mg/kg/d PO x 14d 25 mg base/kg PO in 3 doses over 48 hrs ²²
	OR Quinine sulfate plus doxycycline ^{9,10,11} either followed by primaquine phosphate ²⁰	650 mg PO q8h x 3-7d ⁸ 100 mg PO bid x 7d 30 mg base/d PO x 14d	30 mg/kg/d PO in 3 doses x 3-7d ⁸ 4 mg/kg/d PO in 2 doses x 7d 0.6 mg/kg/d PO x 14d
All <i>Plasmodium</i> species except chloroquine-resistant <i>P. falciparum</i>³ and chloroquine-resistant <i>P. vivax</i>²			
Drug of choice: ⁵	Chloroquine phosphate ²¹	1 g (600 mg base) PO, then 500 mg(300 mg base) 6 hrs later, then 500mg (300 mg base) at 24 and 48 hrs ²²	10 mg base/kg (max. 600 mg base) PO, then 5 mg base/kg 6 hrs later, then 5 mg base/kg at 24 and 48 hrs ²²
PARENTERAL⁴			
All <i>Plasmodium</i> species (Chloroquine-sensitive and resistant)			
Drug of choice: ^{5,23}	Quinidine gluconate ²⁴	10 mg/kg IV loading dose (max. 600 mg) in normal saline over 1-2 hrs, followed by continuous infusion of 0.02 mg/kg/min until PO therapy can be started	10 mg/kg IV loading dose (max. 600 mg) in normal saline over 1-2 hrs, followed by continuous infusion of 0.02 mg/kg/min until PO therapy can be started
	OR Quinine dihydro- chloride ^{24*}	20 mg/kg IV loading dose in 5% dextrose over 4 hrs, followed by 10 mg/kg over 2-4 hrs q8h (max. 1800 mg/d) until PO therapy can be started	20 mg/kg IV loading dose in 5% dextrose over 4 hrs, followed by 10 mg/kg over 2-4 hrs q8h (max. 1800 mg/d) until PO therapy can be started
	OR Artesunate ^{17*}	2.4 mg/kg/dose IV x 3d at 0, 12, 24 and 48 hrs	2.4 mg/kg/dose IV x 3d at 0, 12, 24 and 48 hrs
plus see footnote 19			

* Availability problems. See table below.

- Chloroquine-resistant *P. falciparum* occurs in all malarious areas except Central America (including Panama north and west of the Canal Zone), Mexico, Haiti, the Dominican Republic, Paraguay, northern Argentina, North and South Korea, Georgia, Armenia, most of rural China and some countries in the Middle East (chloro-quine resistance has been reported in Yemen, Oman, Saudi Arabia and Iran). For treatment of multiple-drug-resistant *P. falciparum* in Southeast Asia, especially Thailand, where mefloquine resistance is frequent, atovaquone/proguanil, quinine plus either doxycycline or clindamycin, or artemether/lumefantrine may be used.
- P. vivax* with decreased susceptibility to chloroquine is a significant problem in Papua-New Guinea and Indonesia. There are also a few reports of resistance from Myanmar, India, the Solomon Islands, Vanuatu, Guyana, Brazil, Colombia and Peru (JK Baird et al, Curr Infect Dis Rep 2007; 9:39).
- Chloroquine-resistant *P. malariae* has been reported from Sumatra (JD Maguire et al, Lancet 2002; 360:58).
- Uncomplicated or mild malaria may be treated with oral drugs. Severe malaria (e.g. impaired consciousness, parasitemia >5%, shock, etc.) should be treated with parenteral drugs (KS Griffin et al, JAMA 2007; 297:2264).
- Primaquine is given for prevention of relapse after infection with *P. vivax* or *P. ovale*. Some experts also prescribe primaquine phosphate 30 mg base/d (0.6 mg base/kg/d for children) for 14d after departure from areas where these species are endemic (Presumptive Anti-Relapse Therapy [PART], "terminal prophylaxis"). Since this is not always effective as prophylaxis (E Schwartz et al, N Engl J Med 2003; 349:1510), others prefer to rely on surveillance to detect cases when they occur, particularly when exposure was limited or doubtful. See also footnote 20.
- Although approved for once-daily dosing, Medical Letter consultants usually divide the dose in two to decrease nausea and vomiting.

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MALARIA, Treatment of (continued)

7. Atovaquone/proguanil is available as a fixed-dose combination tablet: adult tablets (*Malarone*; 250 mg atovaquone/100 mg proguanil) and pediatric tablets (*Malarone Pediatric*; 62.5 mg atovaquone/25 mg proguanil). To enhance absorption and reduce nausea and vomiting, it should be taken with food or a milky drink. Safety in pregnancy is unknown; outcomes were normal in 24 women treated with the combination in the 2nd and 3rd trimester (R McGready et al, *Eur J Clin Pharmacol* 2003; 59:545). The drug should not be given to patients with severe renal impairment (creatinine clearance <30mL/min). There have been isolated case reports of resistance in *P. falciparum* in Africa, but Medical Letter consultants do not believe there is a high risk for acquisition of *Malarone*-resistant disease (E Schwartz et al, *Clin Infect Dis* 2003; 37:450; A Farnert et al, *BMJ* 2003; 326:628; S Kuhn et al, *Am J Trop Med Hyg* 2005; 72:407; CT Happi et al, *Malaria Journal* 2006; 5:82).
8. Available in the US in a 324-mg capsule; 2 capsules suffice for adult dosage. In Southeast Asia, relative resistance to quinine has increased and treatment should be continued for 7d. Quinine should be taken with or after meals to decrease gastrointestinal adverse effects.
9. Not FDA-approved for this indication.
10. Use of tetracyclines is contraindicated in pregnancy and in children <8 years old. Tetracycline should be taken 1 hour before or 2 hours after meals and/or dairy products.
11. Doxycycline should be taken with adequate water to avoid esophageal irritation. It can be taken with food to minimize gastrointestinal adverse effects.
12. Oral clindamycin should be taken with a full glass of water to minimize esophageal ulceration.
13. For use in pregnancy and in children <8 yrs.
14. B Lell and PG Kremsner, *Antimicrob Agents Chemother* 2002; 46:2315; M Ramharter et al, *Clin Infect Dis* 2005; 40:1777.
15. At this dosage, adverse effects include nausea, vomiting, diarrhea and dizziness. Disturbed sense of balance, toxic psychosis and seizures can also occur. Mefloquine should not be used for treatment of malaria in pregnancy unless there is no other treatment option because of increased risk for stillbirth (F Nosten et al, *Clin Infect Dis* 1999; 28:808). It should be avoided for treatment of malaria in persons with active depression or with a history of psychosis or seizures and should be used with caution in persons with any psychiatric illness. Mefloquine can be given to patients taking β -blockers if they do not have an underlying arrhythmia; it should not be used in patients with conduction abnormalities. Mefloquine should not be given together with quinine or quinidine, and caution is required in using quinine or quinidine to treat patients with malaria who have taken mefloquine for prophylaxis. Mefloquine should not be taken on an empty stomach; it should be taken with at least 8 oz of water.
16. *P. falciparum* with resistance to mefloquine is a significant problem in the malarious areas of Thailand and in areas of Myanmar and Cambodia that border on Thailand. It has also been reported on the borders between Myanmar and China, Laos and Myanmar, and in Southern Vietnam. In the US, a 250-mg tablet of mefloquine contains 228 mg mefloquine base. Outside the US, each 275-mg tablet contains 250 mg base.
17. The artemisinin-derivatives, artemether and artesunate, are both frequently used globally in combination regimens to treat malaria. Both are available in oral, parenteral and rectal formulations, but manufacturing standards are not consistent (HA Karunajeewa et al, *JAMA* 2007; 297:2381; EA Ashley and NJ White, *Curr Opin Infect Dis* 2005; 18:531). In the US, only the IV formulation of artesunate is available; it can be obtained through the CDC under an IND for patients with severe disease who do not have timely access, cannot tolerate, or fail to respond to IV quinidine (www.cdc.gov/malaria/features/artesunate_now_available.htm). To avoid development of resistance, monotherapy should be avoided (PE Duffy and CH Sibley, *Lancet* 2005; 366:1908). In animal studies, artemisinins have been embryotoxic and caused a low incidence of teratogenicity; no adverse pregnancy outcomes have been observed in limited studies in humans (S Dellicour et al, *Malaria Journal* 2007; 6:15).
18. Artemether/lumefantrine is available as a fixed-dose combination tablet (*Coartem* in countries with endemic malaria, *Riamet* in Europe and countries without endemic malaria); each tablet contains 20 mg artemether and 120 mg lumefantrine (M van Vugt et al, *Am J Trop Med Hyg* 1999; 60:936). It is contraindicated during the first trimester of pregnancy; safety during the second and third trimester is not known. The tablets should be taken with food. Artemether/lumefantrine should not be used in patients with cardiac arrhythmias, bradycardia, severe cardiac disease or QT prolongation. Concomitant use of drugs that prolong the QT interval or are metabolized by CYP2D6 is contraindicated.
19. Adults treated with artesunate should also receive oral treatment doses of either atovaquone/proguanil, doxycycline, clindamycin or mefloquine; children should take either atovaquone/proguanil, clindamycin or mefloquine (F Nosten et al, *Lancet* 2000; 356:297; M van Vugt, *Clin Infect Dis* 2002; 35:1498; F Smithuis et al, *Trans R Soc Trop Med Hyg* 2004; 98:182). If artesunate is given IV, oral medication should be started when the patient is able to tolerate it (SEAQUAMAT group, *Lancet* 2005; 366:717).
20. Primaquine phosphate can cause hemolytic anemia, especially in patients whose red cells are deficient in G-6-PD. This deficiency is most common in African, Asian and Mediterranean peoples. Patients should be screened for G-6-PD deficiency before treatment. Primaquine should not be used during pregnancy. It should be taken with food to minimize nausea and abdominal pain. Primaquine-tolerant *P. vivax* can be found globally. Relapses of primaquine-resistant strains may be retreated with 30 mg (base) x 28d.
21. Chloroquine should be taken with food to decrease gastrointestinal adverse effects. If chloroquine phosphate is not available, hydroxychloroquine sulfate is as effective; 400 mg of hydroxychloroquine sulfate is equivalent to 500 mg of chloroquine phosphate.
22. Chloroquine combined with primaquine was effective in 85% of patients with *P. vivax* resistant to chloroquine and could be a reasonable choice in areas where other alternatives are not available (JK Baird et al, *J Infect Dis* 1995; 171:1678).
23. Exchange transfusion is controversial, but has been helpful for some patients with high-density (>10%) parasitemia, altered mental status, pulmonary edema or renal complications (VI Powell and K Grima, *Transfus Med Rev* 2002; 16:239; MS Riddle et al, *Clin Infect Dis* 2002; 34:1192).
24. Continuous EKG, blood pressure and glucose monitoring are recommended, especially in pregnant women and young children. For problems with quinidine availability, call the manufacturer (Eli Lilly, 800-821-0538) or the CDC Malaria Hotline (770-488-7788). Quinidine may have greater antimalarial activity than quinine. The loading dose should be decreased or omitted in patients who have received quinine or mefloquine. If more than 48 hours of parenteral treatment is required, the quinine or quinidine dose should be reduced by 30-50%.

Information provided by The Medical Letter. For a copy of the entire *Drugs for Parasitic Infections* article, go to: www.medicalletter.org/parasitic_cdc

MANUFACTURERS OF DRUGS USED TO TREAT PARASITIC INFECTIONS

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| albendazole – <i>Albenza</i> (GlaxoSmithKline) | • <i>Biaxin</i> (Abbott) – clarithromycin |
| <i>Albenza</i> (GlaxoSmithKline) – albendazole | § <i>Biltricide</i> (Bayer) – praziquantel |
| <i>Alinia</i> (Romark) – nitazoxanide | † bithionol – <i>Bitin</i> (Tanabe, Japan) |
| <i>Ambisome</i> (Gilead) – amphotericin B, liposomal | † <i>Bitin</i> (Tanabe, Japan) – bithionol |
| amphotericin B – <i>Fungizone</i> (Apothecon), others | § <i>Brolene</i> (Aventis, Canada) – propamidine |
| amphotericin B, liposomal – <i>Ambisome</i> (Gilead) | isethionate |
| <i>Ancobon</i> (Valeant) – flucytosine | chloroquine HCl and chloroquine phosphate – |
| § <i>Antiminth</i> (Pfizer) – pyrantel pamoate | <i>Aralen</i> (Sanofi), others |
| • <i>Aralen</i> (Sanofi) – chloroquine HCl and chloroquine | clarithromycin – <i>Biaxin</i> (Abbott), others |
| phosphate | • <i>Cleocin</i> (Pfizer) – clindamycin |
| § artemether – <i>Artenam</i> (Arenco, Belgium) | clindamycin – <i>Cleocin</i> (Pfizer), others |
| § artemether/lumefantrine – <i>Coartem</i> , <i>Riamet</i> | <i>Coartem</i> (Novartis) – artemether/lumefantrine |
| (Novartis) | <i>crotamiton</i> – <i>Eurax</i> (Westwood-Squibb) |
| § <i>Artenam</i> (Arenco, Belgium) – artemether | dapsone – (Jacobus) |
| § artesunate – (Guilin No. 1 Factory, People's | § <i>Daraprim</i> (GlaxoSmithKline) – pyrimethamine USP |
| Republic of China) | † diethylcarbamazine citrate (DEC) – <i>Hetrazan</i> |
| atovaquone – <i>Mepro</i> n (GlaxoSmithKline) | • <i>Diflucan</i> (Pfizer) – fluconazole |
| atovaquone/proguanil – <i>Malarone</i> | § diloxanide furoate – <i>Furamide</i> (Boots, United |
| (GlaxoSmithKline) | Kingdom) |
| azithromycin – <i>Zithromax</i> (Pfizer), others | doxycycline – <i>Vibramycin</i> (Pfizer), others |
| • <i>Bactrim</i> (Roche) – TMP/Sulfa | eflornithine (Difluoromethylornithine, DFMO) – |
| § benznidazole – <i>Rochagan</i> (Brazil) | <i>Ornidyl</i> (Aventis) |

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- § *Egaten* (Novartis) – triclabendazole
 § *Elimite* (Allergan) – permethrin
 § *Ergamisol* (Janssen) – levamisole
 § *Eurax* (Westwood-Squibb) – crotamiton
- *Flagyl* (Pfizer) – metronidazole
- § *Flisint* (Sanofi-Aventis, France) – fumagillin
 § fluconazole – *Diflucan* (Pfizer), others
 § flucytosine – *Ancobon* (Valeant)
- § fumagillin – *Flisint* (Sanofi-Aventis, France)
- *Fungizone* (Apothecon) – amphotericin
- § *Furamide* (Boots, United Kingdom) – diloxanide furoate
- § furazolidone – *Furozone* (Roberts)
- § *Furozone* (Roberts) – furazolidone
- † *Germanin* (Bayer, Germany) – suramin sodium
- § *Glucantime* (Aventis, France) – meglumine antimonate
- † *Hetrazan* – diethylcarbamazine citrate (DEC)
Humatin (Monarch) – paromomycin
- § *Impavido* (Zentaris, Germany) – miltefosine
 § iodoquinol – *Yodoxin* (Glenwood), others
 § itraconazole – *Sporanox* (Janssen-Ortho), others
 § ivermectin – *Stromectol* (Merck)
 § ketoconazole – *Nizoral* (Janssen), others
- † *Lampit* (Bayer, Germany) – nifurtimox
- § *Lariam* (Roche) – mefloquine
- § *Leshcutan* (Teva, Israel) – topical paromomycin
 § levamisole – *Ergamisol* (Janssen)
 § lumefantrine/artemether – *Coartem*, *Riamet* (Novartis)
 § *Malarone* (GlaxoSmithKline) – atovaquone/proguanil
 § malathion – *Ovide* (Medicis)
 § mebendazole – *Vermox* (McNeil), others
 § mefloquine – *Lariam* (Roche)
- § meglumine antimonate – *Glucantime* (Aventis, France)
- † melarsoprol – *Mel-B*
- † *Mel-B* – melarsoprol
- § *Mepro*n (GlaxoSmithKline) – atovaquone
 § metronidazole – *Flagyl* (Pfizer), others
- § miconazole – *Monistat i.v.*
- § miltefosine – *Impavido* (Zentaris, Germany)
- § *Monistat i.v.* – miconazole
- § *NebuPent* (Fujisawa) – pentamidine isethionate
- § niclosamide – *Yomesan* (Bayer, Germany)
- † nifurtimox – *Lampit* (Bayer, Germany)
 § nitazoxanide – *Alinia* (Romark)
 § *Nix* (GlaxoSmithKline) – permethrin
- *Nizoral* (Janssen) – ketoconazole
- § ornidazole – *Tiberal* (Roche, France)
 § *Ornidyl* (Aventis) – eflornithine (Difluoromethylornithine, DFMO)
 § *Ovide* (Medicis) – malathion
- § oxamniquine – *Vansil* (Pfizer)
- § *Paludrine* (AstraZeneca, United Kingdom) – proguanil
 § paromomycin – *Humatin* (Monarch); *Leshcutan* (Teva, Israel; topical formulation not available in US)
 § *Pentam 300* (Fujisawa) – pentamidine isethionate
 § pentamidine isethionate – *Pentam 300* (Fujisawa), *NebuPent* (Fujisawa)
- † *Pentostam* (GlaxoSmithKline, United Kingdom) – sodium stibogluconate
 § permethrin – *Nix* (GlaxoSmithKline), *Elimite* (Allergan)
- § praziquantel – *Biltricide* (Bayer)
- § primaquine phosphate USP
- § proguanil – *Paludrine* (AstraZeneca, United Kingdom)
 § proguanil/atovaquone – *Malarone* (GlaxoSmithKline)
- § propamidine isethionate – *Brolene* (Aventis, Canada)
- § pyrantel pamoate – *Antiminth* (Pfizer)
 § pyrethrins and piperonyl butoxide – *RID* (Pfizer), others
- § pyrimethamine USP – *Daraprim* (GlaxoSmithKline)
 § *Qualaquin* – quinine sulfate (Mutual Pharmaceutical Co/AR Scientific)
 § quinacrine
- * quinidine gluconate (Eli Lilly)
- § quinine dihydrochloride
 § quinine sulfate – *Qualaquin* (Mutual Pharmaceutical Co/AR Scientific)
 § *Riamet* (Novartis) – artemether/lumefantrine
- *RID* (Pfizer) – pyrethrins and piperonyl butoxide
 - *Rifadin* (Aventis) – rifampin
 § rifampin – *Rifadin* (Aventis), others
- § *Rochagan* (Brazil) – benznidazole
- * *Rovamycine* (Aventis) – spiramycin
- † sodium stibogluconate – *Pentostam* (GlaxoSmithKline, United Kingdom)
- * spiramycin – *Rovamycine* (Aventis)
 - *Sporanox* (Janssen-Ortho) – itraconazole
 § *Stromectol* (Merck) – ivermectin
 § sulfadiazine – (Eon)
- † suramin sodium – *Germanin* (Bayer, Germany)
- § *Tiberal* (Roche, France) – ornidazole
 § *Tindamax* (Mission) – tinidazole
 § tinidazole – *Tindamax* (Mission)
 § TMP/Sulfa – *Bactrim* (Roche), others
- § triclabendazole – *Egaten* (Novartis)
- § *Vansil* (Pfizer) – oxamniquine
- *Vermox* (McNeil) – mebendazole
 - *Vibramycin* (Pfizer) – doxycycline
 - *Yodoxin* (Glenwood) – iodoquinol
 - § *Yomesan* (Bayer, Germany) – niclosamide
 - *Zithromax* (Pfizer) – azithromycin

* Available in the US only from the manufacturer.

§ Not available commercially. It may be obtained through compounding pharmacies such as Panorama Compounding Pharmacy, 6744 Balboa Blvd, Van Nuys, CA 91406 (800-247-9767) or Medical Center Pharmacy, New Haven, CT (203-688-6816). Other compounding pharmacies may be found through the National Association of Compounding Pharmacies (800-687-7850) or the Professional Compounding Centers of America (800-331-2498, www.pccarx.com).

† Available from the CDC Drug Service, Centers for Disease Control and Prevention, Atlanta, Georgia 30333; 404-639-3670 (evenings, weekends, or holidays: 770-488-7100).

• Also available generically.