Revised & Approved

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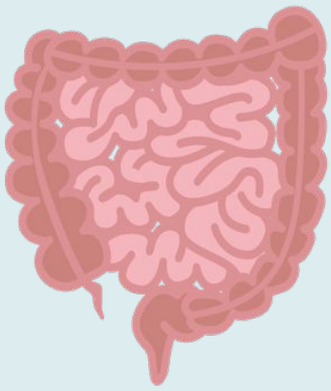
Pharmacology 439

MED439
KING SAUD UNIVERSITY



Gastrointestinal Block

Pharmacology Team 439

Helpful video

**Color index:**

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

# Antiprotozoal /Antimalarial Drugs

**We highly recommend studying microbiology of malaria and watching plasmodium species (Malaria) from osmosis before this lecture**

## Objectives:

1- Classify the main antimalarial drugs depending on their goal of therapy.
2- Detail the pharmacokinetics and dynamics of main drugs used to treat attack or prevent relapses.
3- State the WHO therapeutic strategy for treatment.
4- Hint on the CDC recommendations for prophylaxis in travelers to endemic areas.

Editing file | Summary

**According to WHO:**

- 212 million cases of malaria worldwide in 2015 and 429,000 deaths. 90% of malaria cases and deaths occur in Africa.
- Children under 5 are most at risk.

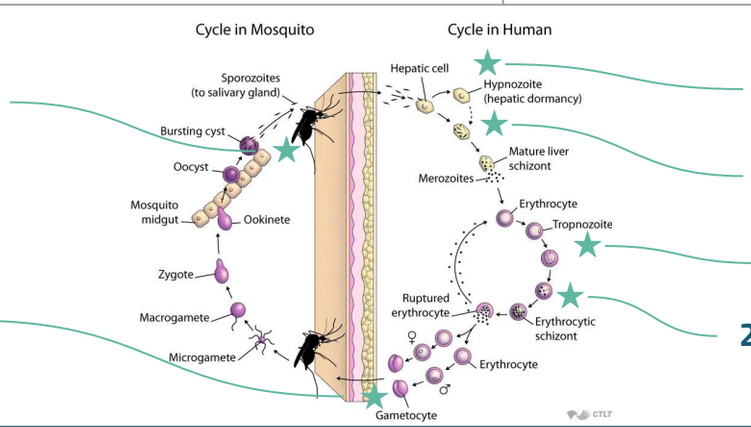
**Four species of plasmodium typically cause human malaria:**

1- P. falciparum (Most dangerous) 2- P. vivax 3- P. malariae 4- P. ovale

# ★ Therapeutic classification:

Female DR: focus on the summaries at the beginning and end to memorize each drug and during which stage we can use it.
**Microbiology of malaria and Pharmacology of malaria may come as combined question in SAQs**

| Class | Drug | M.O.A / USES |
|---|---|---|
| **1- Causal prophylaxis** | - Prima**quine** | Destroys parasite in **liver cells** (hypnozoite) and prevent invasion of **erythrocytes** |
| **2- Suppressive prophylaxis** | - Chloro**quine**<br>- Meflo**quine**<br>- Doxy**cycline** (Abx) | Suppresses the **erythrocytic phase** and thus attack of malaria fever (destroy schizonts before symptoms) |
| **3- Clinical cure (Erythrocytic schizonticide)** | **Fast acting high efficacy** (used in severe cases)**:**<br>- Chloro**quine**<br>- Quinine<br>- Meflo**quine**<br>- Artemisinin | Used to terminate an episode of malarial fever (kill blood schizont before rupture) |
| | **Slow acting low efficacy:**<br>- Pyrimethamine (abx)<br>- Proguanil<br>- Sulfonamides (abx) | |
| **4- Radical cure** | Suppressive drug (listed above as number 2) + Hypnozoitocidal (primaquine) | Eradicate **all forms** of plasmodium vivax from the body |
| **5- Gametocidal efficacy** | **Against vivax:**<br>- Chloro**quine**<br>- Quinine | Destroys **gametocytes** and prevent transmission into the mosquito |
| | **Against all species:**<br>- Prima**quine** | |
| **6- Sporozoitocides** | - Proguanil<br>- Pyrimethamine | Destroys **sporozoites** |




**6- Sporozoitocides**

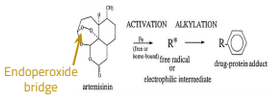
**5- Gametocidal**

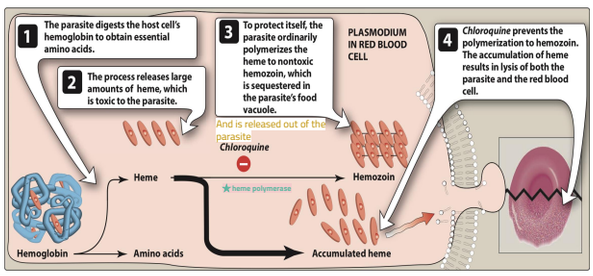
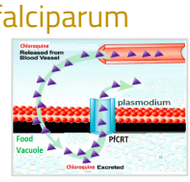
**1- Causal prophylaxis**

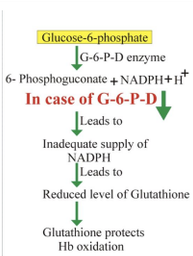
**4- Radical cure**

**3- Clinical cure**

**2- Suppressive prophylaxis**

| Drug | **Artemisinin** |
|---|---|
| About | • Artemisinin is the active principle of the plant Artemisia annua (qinghaosu)<br>• Advantages:<br>- Affect **all forms** including multidrug resistant P. falciparum.<br>- Fast acting **blood Schizonticide** (not active against hypnozoites).<br>• Disadvantages:<br>- Short duration of action.<br>- High recrudescence (recurrence) rate after short-course therapy (recurrence of symptoms because there is still dormant parasite in the liver).<br>  |
| M.O.A | • *Artemisinin* and its analogs are very rapidly acting blood schizonticides against all human malaria parasites. **No effect on hepatic stages.**<br>• They have **endoperoxide bridges,** Haem iron cleaves this bridge to yield carbon-centered free radicals in parasite, that will:<br>- Alkylate (binds to) membranes of parasite's **food vacuole** and mitochondria → **no energy.**<br>- Irreversibly bind and inhibit sarco-endoplasmic reticulum **$Ca^{2+}$-ATPase** of the parasite → thereby **inhibiting its growth.**<br>- Inhibiting formation of **transport vesicles** → **no food vacuoles.**<br>  <br>  |
| P.K | • *Artemisinin, artesunate, artemether* are **pro**drugs<br>• Rapidly biotransformed in liver into dihydroartemisinin → more **active** metabolite<br>• Poorly soluble in water and oil, can only be used orally (another disadvantage).<br>• Derivatives *(artesunate, artemether)* are rapidly absorbed orally and Widely distributed<br>• t½:<br>- ***Artemisinin***: 4 hrs<br>- ***Artesunate***: 45 min (disadvantage), (water-soluble; oral, IV, IM, rectal administration) (advantage).<br>- **Artemether**: 4-11 hrs, (lipid-soluble; oral, IM, and rectal administration). **Induce its own CYP-mediated metabolism→ ↑ clearance 5 fold** (disadvantage). |
| Uses | • Because **artemisinin derivatives** have short t½ the solution is either:<br>- Monotherapy should be extended beyond disappearance of parasite and symptoms to prevent recrudescence.<br>or<br>- By combining the drug with long- acting antimalarial drugs (Ex. *mefloquine*). |
| ADRs | • Nausea and vomiting, which can be confused with malaria symptoms.<br>• Transient heart block.<br>• Decrease neutrophil count (Neutropenia) (rare).<br>• Brief episodes of fever (causes confusion of whether it's from the drug or malaria).<br>• Resistance → was reported recently in Cambodia- Thailand border. |
| **Pre-paration** | • ***Artesunate*** IV or IM preparations for severe complicated cases as cerebral malaria (given for 24h only because of ↑ risk of side effects) followed by complete course of ACT.<br>• Artemisinin-based combination therapies (ACTs) (artemether+long acting anti malaria drugs)(one day IV injection then oral ACT combination):<br>- *Artemether + lumefantrine*<br>- *Artemether + amodiaquine*<br>- *Artemether + mefloquine*<br>- *Artemether +* (*sulfadoxine - pyrimethamine*) |

| Drug | **Chloroquine** |
|---|---|
| About | • Cheap so it's frequently used.<br>• Potent **blood Schizonticide.**<br>• Active against **all forms** of the schizonts (**exception** is chloroquine-resistant P.f. and P.v.).<br>• **Not** active against tissue schizonts.<br>• **Gametocide**: Against **all** species (**except** P. falciparum). |
| M.O.A | • Malaria Parasite digest host cell's Hb to utilize globin and obtain amino acids.<br>• Heme is released (Toxic to the parasite) → so parasite detoxifies (polymerize) it by **heme polymerase** enzyme → Hemozoin (Non Toxic) and traps it in food vacuoles.<br>• Chloroquine blocks **heme polymerase** enzyme leads to accumulation of heme results in lysis of the parasite and the RBCs.<br>  |
| P.K | • Rapidly and completely absorbed from the GIT, given orally.<br>• Has high volume of distribution (100-1000 L/kg); Released slowly from tissues and metabolized in liver.<br>• Concentrated into parasitized RBCs.<br>• Excreted in the urine 70% unchanged.<br>• 2 compartment model t½: **1)** Initial t½ (the time needed for the drug to be distributed from the blood to the tissues) = 2-3 days and **2)** terminal elimination t½ (the time needed for the drug to be excreted from the whole body ) =1-2 months (because of ↑ Vd and tissue accumulation). |
| Uses | • Used to eradicate **blood schizonts of Plasmodium** (used as a rapid cure and prophylaxis).It is given in loading dose to rapidly achieve effective plasma concentration.<br>• Hepatic amebiasis. remember dysentery and amoebiasis lecture?<br>• Rheumatoid arthritis.<br>• **Safe in pregnancy.**<br>• Has antipyretic effect. |
| ADRs | • Short period of treatment:<br>- Mild headache and visual disturbances.<br>- GIT upsets; Nausea and vomiting.<br>- Pruritus (itch) and urticaria (hives).<br>• **Prolonged therapy and high doses:** (could happen to a patient with Rheumatoid arthritis since they're treated by chloroquine for a long time).<br>- **Ocular toxicity**: Loss of accommodation, lenticular opacity and retinopathy.<br>- Ototoxicity.<br>- Weight loss.<br>- Bolus injection (not recommended) → hypotension and dysrhythmias. |
| **Resistance** | • Resistance against the drug develops as a result of mutation of the plasmodium falciparum chloroquine resistance transporter (**PfCRT**)<br>• Chloroquine enters parasite through food vacuole. **PfCRT** enhances the efflux of chloroquine from the food vacuole.<br>  <br>There are some drugs that can block these channels, such as verapamil, imipramine and antihistamines, but they have high VOD and narrow therapeutic index. Using a combination of them is a potential way to overcome resistance. |

| Drug | Quinine |
|---|---|
| M.O.A | • Same as chloroquine. |
| P.K | • The main alkaloid in cinchona bark (another alkaloid is *quinidine* which is more toxic and is an isomer of *quinine*. It is claimed that *Quinidine* is more potent than *Quinine*).  <br>• Potent **blood Schizonticide** of all malarial parasites and gametocide for P.vivax and ovale but **not** falciparum. **It is Not active against liver stage parasites.**<br>• Depresses the myocardium, reduce excitability and conductivity (by affecting Na channels).<br>• Mild analgesic, antipyretic, stimulation of uterine smooth muscle (these serve as other uses for quinine), **curare mimetic effect** (it's muscle relaxant and has neuromuscular blocking efficacy so not given to people with NMJ problems).<br>• Rapidly and completely absorbed from the GIT.<br>• Peaks after 1-3 hours.<br>• Metabolized in the liver and excreted in urine.<br>• 5-20% excreted in the urine unchanged. Because it is excreted partially in urine, and also because it has active metabolite (Hydroxyquinine); we must reduce the dose in patients with renal failure.<br>• T½ = 10 hrs but longer in severe falciparum infection (18 hrs).<br>• Administered: orally in a 7 day course or by slow IV for severe P.falciparum infection. |
| Uses | • Parenteral treatment of **severe** falciparum malaria (slowly with cardiac monitoring due to higher risk of arrhythmia).<br>• Oral treatment of falciparum malaria. (Schizontocides).<br>• Nocturnal leg cramps. off-label use (given before sleep).<br>• Safe in pregnancy. |
| ADRs | • With therapeutic dose:<br>- Poor compliance → bitter taste (that's why in some countries they add it to soft drinks to encourage people to drink it).<br>• With Higher doses:<br>- **Cinchonism** (a collection of side effects- giving it its name because *quinine* is extracted from cinchona bark)→ (tinnitus, deafness, headaches, nausea and visual disturbances).<br>• Abdominal pain and diarrhea, Rashes, fever, hypersensitivity reactions, Hypotension and arrhythmias, **hypoglycemia** (by increasing insulin release).<br>• Blood dyscrasias (blood disorders); **anaemia**, thrombocytopenic purpura and hypoprothrombinemia (mild).<br>• Blackwater fever: a fatal condition in which acute haemolytic anaemia is associated with renal failure due to a hypersensitivity reaction to the drug.<br>- Blackwater fever is caused due to:<br>1. Its chemical structure.<br>2. Renal failure.<br>3. Hemolytic anemia, It is thought that it happens only to people allergic to *Quinine*.<br>• IV neurotoxicity → tremor of the lips and limbs, delirium, fits, stimulation followed by depression of respiration and coma.<br>• Safe in pregnancy (doesn't cross placenta or affect growth of fetus). |
| C.I | • **Prolonged QT Interval** (arrhythmic patient).<br>• **G6PD deficiency**.<br>• Myasthenia Gravis. Due to its muscle relaxant effects<br>• Hypersensitivity.<br>• Optic Neuritis and auditory problems.<br>• Dose should be reduced in renal insufficiency.   |

| Drug | **Quinine** |
|---|---|
| Drug interactions | • Antacids: Antacids containing aluminum and/or magnesium because they bind to *quinine* ⟶ may delay or decrease absorption of *quinine*.<br>• *Mefloquine* (because both **prolong QT interval** - given together may cause heart block).<br>• *Quinine* can raise plasma levels of *warfarin* and *digoxin* (which have low therapeutic index) by inhibiting their excretion. |
| **Resistance** | • Like *chloroquine*, by mutation of chloroquine resistance transporter (PfCRT), also increased expression of P-glycoprotein transporter⟶ efflux of drug out of parasite. |

| Drug | **Primaquine** |
|---|---|
| M.O.A | • Not well understood, It may be acting by:<br>- **Generating ROS** (=electrophiles) ⟶ can damage lipids, proteins and nucleic acids in the parasite.<br>- Interfering with the electron transport ⟶ no energy.<br>- Inhibiting formation of transport vesicles ⟶ no food vacuoles. |
| P.K | • Well absorbed orally.<br>• **Rapidly metabolized to *etaquine* and *tafenoquine* ⟶ more active forms.** *etaquine* and *tafenoquine* can be used as standalone drugs.<br>• T½ 3-6 h. |
| P.D | • Hypnozoitocides, the only one **against liver hypnozoites.** (Dormant stage)<br>• Gametocytocidal, **against the 4 human malaria species.**<br>• Radical cure of P. ovale and P. vivax.<br>• Prevent spread of ALL forms (chemoprophylaxis). (Because it destroys the Gametes) |
| Uses | • Radical cure of relapsing malaria, **15 mg/day for 14 days** (the standard dose).<br>(After a drug that kills the parasites in the blood is given we give primaquine to kill dormant parasites in the liver).<br>• In falciparum malaria: a single dose (45 mg) to kill gametes and cut down transmission. |
| **Doses**<br>(Female DR: memorize them) | • G-6-PD **normal** ⟶ 15 mg\day for **14 days.**<br>• G-6-PD **deficiency** (**mild**-moderate African form) ⟶ 45 mg\week **for 8 weeks.**<br>• G-6-PD **deficiency** (more **severe** mediterranean variety) ⟶ 30 mg\week **for 30 weeks.** |
| ADRs | • **At regular doses:**<br>- Patients with G-6-PD deficiency ⟶ hemolytic anemia.<br>- Oxidation of *primaquine* produces free radicals ⟶ Free radicals will cause oxidative damage of RBCs ⟶ Hemolysis. More likely to cause hemolysis than *Quinine.*<br>- $H_2O_2$ oxidizes GSH.<br>- GSH Maintains integrity of RBCs.<br>• **At larger doses:**<br>- Epigastric distress and abdominal cramps.<br>- Mild anemia, cyanosis (due to methemoglobinemia) and methemoglobinemia.<br>- Severe methemoglobinemia rarely in patients with deficiency of NADPH methemoglobin reductase.<br>- Granulocytopenia and agranulocytosis rare. |
| C.I | • Should be **avoided** in pregnancy:<br>- (the fetus is relatively G6PD-deficient and thus at risk of hemolysis).<br>• Should be **avoided** in G6PD deficiency patients. But because there are no alternatives, in case of P.vivax or P.ovale we give it in modified dose and monitor hemolysis |
| **Resistance** | • Rare when *primaquine* and *chloroquine* are combined (we combine them together to prevent resistance). |

# ★ Who treatment guidelines

**Uncomplicated**:
- ACT

**Complicated**:
- IV Artesunate for 24 hrs followed by ACT
- or Artemether + [Clindamycin / doxycycline]
- or Quinine + [Clindamycin / doxycycline]

**In Plasmodium. vivax**

**In Plasmodium. falciparum**
**(All show Resistance)**

**If Sensitive** :
- Chloroquine for 3 days followed by Primaquine for 14 days

**If Resistant** :
- ACT / 3 days followed by Primaquine for 14 days.

**For P.falciparum**

**Special risk group**

- Pregnancy (**2nd and 3rd trimester**)
- Lactating women Infants and young children (<2 years ): ACT

- Pregnancy (**1st trimester**): Quinine + Clindamycin (7 days)

- After baby is delivered, breastfeeding is done, children grow (we should follow up with primaquine).

# ★ Prophylaxis in travelers

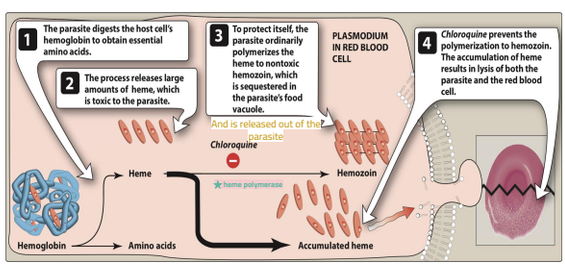
1. **Chloroquine**
   Areas without resistant P. falciparum

2. **Mefloquine**
   Areas with chloroquine- resistant P. falciparum

3. **Doxycycline**
   Areas with multidrug-resistant P falciparum

Begin 1-2 weeks before departure (except for doxycycline 2 days) and continue for 4 weeks after leaving the endemic area.

# Summary

| Drug | M.O.A | Uses | ADRs<br>D.I |
|---|---|---|---|
| **Artemisinin** | • They have **endoperoxide bridges,** Haem iron cleaves this bridge to yield carbon-centered free radicals in parasite, that will:<br>- Alkylate membranes of parasite's **food vacuole** and mitochondria → **no energy.**<br>- Irreversibly bind and inhibit sarco-endoplasmic reticulum **Ca2+ -ATPase** of the parasite → thereby **inhibiting its growth.**<br>- Inhibiting formation of **transport vesicles** → **no food vacuoles.** | • Monotherapy should be extended beyond disappearance of parasite to prevent Recrudescence .<br><br>• Combining the drug with long- acting antimalarial drugs (Ex. *mefloquine*). | • Transient heart block<br>• ↓ neutrophil count (rare)<br>• Brief episodes of fever<br>• Resistance |
| **Chloroquine** | • prevents the polymerization of heme to hemozoin by **inhibiting Heme Polymerase enzyme** and the accumulation of heme results in lysis of the parasite. | • eradicate blood schizonts of Plasmodium.<br>• Hepatic amebiasis.<br>• Rheumatoid arthritis.<br>• **Safe in pregnancy.** | • Mild headache and visual disturbances<br>• GIT upsets; Nausea and vomiting<br>• Pruritus and urticaria<br><br>**Prolonged therapy and high doses:**<br>• **Ocular toxicity**<br>• Ototoxicity<br>• Weight loss<br>• Bolus injection → hypotension and dysrhythmias |
| **Quinine** |  | • Parenteral treatment of **severe** falciparum malaria.<br>• Oral treatment of falciparum malaria.<br>• Nocturnal leg cramps.<br>• **Safe in pregnancy.** | • With Higher doses □: Cinchonism □→ (tinnitus, deafness, headaches, nausea and visual disturbances)<br>• Blood dyscrasias; **anaemia**, thrombocytopenic purpura and hypoprothrombinemia<br>• Blackwater fever<br>•if given IV □it causes neurotoxicity: tremor of the lips and limbs, delirium, fits, stimulation followed by depression of respiration and coma |
| **Primaquine** | • **Generating ROS** □→ can damage lipids, proteins and nucleic acids in the parasite.<br>• Interfering with the electron transport □no energy.<br>• Inhibiting formation of transport vesicles □no food vacuoles. | • **Against the 4 human malaria species**<br>• Radical cure of P. ovale and P. vivax<br>• Prevent spread of ALL forms (chemoprophylaxis) | • At regular doses:<br>- Patients with G-6-PD deficiency □→ hemolytic anemia<br>- Produces free radicals → will cause oxidative damage of RBCs → Hemolysis<br>• At larger doses:<br>- Epigastric distress and abdominal cramps<br>Mild anemia, cyanosis and methemoglobinemia<br>• **C.I: pregnancy and G6PD deficiency** |

# MCQs

| | | | |
|---|---|---|---|
| Q1: Which drug should be given later to eradicate schizonts and latent and hypnozytes in the patient's liver ? | | | |
| A- Quinine | B-Primaquine | C-Artesunate | D-Chloroquine |
| Q2: Plasmodial resistance to chloroquine is due to ? | | | |
| A- Decreased accumulation of the drug in the food vacuole | B-Increased activity of DNA repair mechanisms | C-Induction of drug-inactivating enzymes | D-Change in receptor structure |
| Q3: A patient with glucose-6-phosphate dehydrogenase (G6PD) deficiency presents for advice about malaria prophylaxis He is about to go on a 'gap year during which he will be travelling abroad for 12 months. Which one of the following medications is it **most important that he avoids** ? | | | |
| A- Quinine | B- Chloroquine | C- Artemisinin | D- Primaquine |
| Q4: Shatha is planning to go on vacation to africa, an area with chloroquine- resistant P. falciparum, what does she take to protect herself ? | | | |
| A- Quinine | B- Mefloquine | C- Primaquine | D- Artemether |
| Q5: Which of the following is appropriate anti-malarial therapy for a pregnant women in her 1st trimester ? | | | |
| A- Artemether + Doxycycline | B-Artemether + lumefantrine | C-Quinine + Clindamycin | D-Chloroquine primaquine |
| Q6: A patient on warfarin was given anti-malaria drug, after a few days the prothrombin time become significantly prolonged, which one of following antimalarial drug cause this ADRs ? | | | |
| A- Quinine | B- Primaquine | C-Chloroquine | D-Artemether |
| Q7: Turkish child with severe G6PD deficiency who has infected by malaria which is resistant for chloroquine and artemether Which one of the following doses is required to eradicate them by primaquine ? | | | |
| A- 15 mg\day for 14 days. | B-45 mg\week for 8 weeks. | C-30 mg\week for 30 weeks. | D- 50 mg\week for 30 weeks |
| Q8: Which one of the following antimalarial drugs can cause Blackwater fever as serious adverse effect ? | | | |
| A- Chloroquine | B-Quinine | C-Primaquine | D-Mefloquine |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|
| B | A | D | B | C | A | C | B |

# SAQ

**Q1) Mention M.O.A of Chloroquine**

**Q2) List 3 side effects of primaquine**

**Q3) List 4 C.I of Quinine**

**Q4) 3 uses of chloroquine**

**Q5) List 3 side effects of artemisinin**

# Answers

A1) Page4

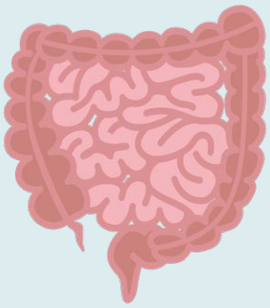
A2) Abdominal cramps, Hemolysis, Cyanosis

A3) Hypersensitivity, Prolonged QT interval, Optic neuritis, Myasthenia gravis

A4) Hepatic amebiasis, Rheumatoid arthritis, Used to eradicate **blood schizonts of Plasmodium**

A5) Transient heart block, Reduce neutrophils count , Brief episodes of fever

Feedback Form



# Gastrointestinal Block

Pharmacology Team 439

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