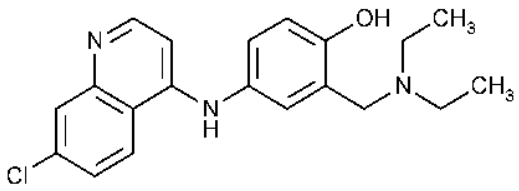
BASOQUIN®
(Amodiaquine)

1. NAME OF THE MEDICINAL PRODUCT

Basoquin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Structural Formula of Amodiaquine:



Amodiaquine Hydrochloride is the hydrochloride salt of amodiaquine, an orally active 4-aminoquinoline derivative with antimalarial and anti-inflammatory properties. Similar in structure and activity to chloroquine, amodiaquine is effective against some chloroquine-resistant strains, particularly *Plasmodium falciparum*, the most deadly malaria parasite.[1]

Each tablet contains 150 mg amodiaquine (camoquin) base (P.D.)

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Amodiaquine (AQ) in combination with artesunate is indicated for the treatment of uncomplicated **P. falciparum or P. vivax malaria** and is considered to be effective against **P. ovale, P. knowlesi and P. malariae.**[2]

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Adults

In partially immune subject: Four tablets (600 mg) as a single dose.

In non-immune subject: Four tablets (600 mg) as a single dose on each of three successive days.

4.3. CONTRAINDICATIONS

Amodiaquine should not be prescribed in the following conditions:

Hypersensitivity to 4-aminoquinoline derivative.[9]
Hepatotoxicity; as amodiaquine may concentrate in the liver, the drug should be used with caution in patients with hepatic disease or alcoholism, and in patients receiving hepatotoxic drugs.[5]

It is contraindicated in patients with **Liver Disease**, **Neutropenia and Retinopathy**

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE[14]

Caution should be exercised in patients with G6pD deficiency, nerve disease, any allergy, kidney or liver impairment, during pregnancy and breastfeeding.

Avoid long-term use of this medication; otherwise vision loss may occur.

As amodiaquine may concentrate in liver, the drug should be used with caution in patients with hepatic disease and patient receiving hepatotoxic drugs.[15]

Serum ALT levels should be measured in every patient taking the drug who has asthenia and vomiting.[16]

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Demonstrated interactions:

- Increased plasma concentration and elevated liver enzyme activities when given in combination with efavirenz.
- Decreased plasma concentration with nevirapine.
- Increased risk for neutropenia with zidovudine-containing regimens and trimethoprim plus sulfamethoxazole.[2]

Potential interactions:

- Increased risk for cardiac events with anti-arrhythmic agents.
- Visual loss or disturbances with mefloquine.
- Recommended to use with caution with inhibitors of CYP2C8 and CYP2A6.
- Amodiaquine may inhibit CYP2D6 and CYP2C9.[2]

Since magnesium trisilicate and kaolin are known to decrease the gastrointestinal absorption of chloroquine when administered simultaneously, it is likely that this also follows for amodiaquine. Concomitant administration of chloroquine at recommended doses for malaria suppression of chemoprophylaxis during pre-exposure prophylaxis of rabies with intra-dermally administered rabies vaccine may interfere with the antibody response to the vaccine. However, the clinical significance of this interaction remains to be clearly established but should be considered and may have relevance in the case of amodiaquine.[5]

4.6. FERTILITY, PREGNANCY AND LACTATION

Usage in Pregnancy

The available data suggest that, at standard dosages, amodiaquine is not teratogenic and that the adverse events associated with taking amodiaquine in pregnancy are not greater than those associated with falciparum malaria in pregnancy.

No serious adverse events of AQ following its use in pregnancy have been reported, although adverse events were not systematically looked for in earlier studies, which were not designed specifically to assess safety of the drug in pregnancy. The recent study in Ghana was the first to address this issue in a reasonable number of pregnant women and it showed no serious toxicity of AQ.[10]

No significant changes in the pharmacokinetics of amodiaquine or its metabolite desethylamodiaquine have been observed during the second and third trimesters of pregnancy; therefore, no dosage adjustments are recommended.[2,11]

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No information is available.

4.8. UNDESIRABLE EFFECTS

Oral administration of a single dose of amodiaquine may be followed by **abdominal discomfort, nausea, vomiting, headache, dizziness, blurring of vision, mental and physical weakness, and fatigue**. These symptoms are usually mild and transient.

More severe adverse reactions include; **itching, cardiovascular abnormalities, dyskinesia, ocular damage, neuromuscular disorders and hearing loss**.

There have been several reports of agranulocytosis and these have limited its use in prophylaxis.[5] Amodiaquine + SP (Sulfadoxine-pyrimethamine), is generally well tolerated in children, and no serious adverse events have been reported.[2]

Amodiaquine Toxicity:

Because the 4-aminoquinoline derivatives are rapidly and completely absorbed from the GI tract, symptoms of acute toxicity may occur within 30 minutes following ingestion of the drugs.[5]

Hepatotoxicity:

Amodiaquine has been linked to serum aminotransferase elevations in a small proportion of patients (1%), and causes severe cases of acute hepatitis which can be fatal, for which reason it is recommended for use only as treatment and not for prophylaxis against malaria.[12] High total doses or prolonged duration of treatment, or both, appear to favor the occurrence of agranulocytosis and liver damage.[13] The onset is usually within 1 to 4 months.[12]

The pattern of serum enzyme elevations is most frequently hepatocellular, and symptoms resembling acute viral hepatitis are typical. Features of hypersensitivity are uncommon, as are autoantibodies. The hepatitis can be severe, and several fatal instances or cases requiring emergency liver

transplantation have been reported. The frequency of serious hepatic injury is estimated to be ~1:15,000.[12]

4.9. OVERDOSE

Avoid excess dosage; Symptoms of over dosage of 4-aminoquinoline derivatives include headache, drowsiness, visual disturbances, nausea, vomiting, cardiovascular collapse, and seizures followed by sudden and early respiratory and cardiac arrest. Hypotension, if not treated, may progress rapidly to shock. Electrocardiograms (ECG) may reveal atrial standstill, nodal rhythm, prolonged intraventricular conduction time, and progressive bradycardia leading to ventricular fibrillation and/or arrest.[9]

Reported Fatal Dose:

It is likely that the fatal dose for amodiaquine would be similar to that of chloroquine phosphate (2 to 3 g, adult) since amodiaquine appears to completely parallel the adverse effects of those seen with chloroquine when equivalent doses are used.[9]

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Amodiaquine is a Mannich base 4-aminoquinoline that is similar in structure and mechanism of action to chloroquine. Amodiaquine is converted to its active metabolite desethylamodiaquine and is thought to act by accumulating inside the parasite food vacuole and interfering with haem detoxification.

The drug also inhibits the glutathione-dependent destruction of ferriprotoporphyrin IX in the malaria parasite, resulting in the accumulation of this peptide, which is toxic for the parasite. Amodiaquine is effective against some parasite strains that are resistant to chloroquine, although some cross-resistance exists.[2]

5.2. PHARMACOKINETIC PROPERTIES

After oral administration of AQ (600 mg), absorption of AQ is rapid, reaching peak concentrations in plasma, whole blood, and packed cells at 0.5 +/- 0.03, 0.5 +/- 0.1 and 0.5 +/- 0.1 h respectively (mean +/- s.e. mean).[3]

Amodiaquine hydrochloride is readily absorbed from the gastrointestinal tract.

Amodiaquine is rapidly converted in the liver, via the cytochrome P450 isoenzyme CYP2C8, to the active metabolite desethylamodiaquine, only a negligible amount of amodiaquine being excreted unchanged in the urine[4] and little of the parent compound is present in the blood.[5]

The apparent terminal half-life of amodiaquine after oral administration is 5.2 + 1.7 (range 0.4 to 5.5) minutes and the geometric mean of the estimated elimination phase half-lives is 2.1 (range 0.5 to 5.7) hours.[4]

The plasma elimination half-life of desethylamodiaquine has varied from 1 to 10 days or more.[4]

Amodiaquine and desethylamodiaquine have been detected in the urine several months after use.[4]

Pharmacokinetic parameters reported for amodiaquine and its active metabolite desethylamodiaquine in studies of currently recommended dosages for treatment of uncomplicated malaria or seasonal malaria chemoprevention (range of mean or median values reported)

Parameter	Amodiaquine	Desethylamodiaquine
C_{max} (ng/mL)	5.2–39.3	161–751
T_{max} (h)	0.5–2.0	2.71-47.9
Elimination $T_{1/2}$ (h)	3.3–12.4	90–240
Vd/f (L/kg)	311–1010	62.4–252
Cl/f (L/h per kg)	14–57.8	0.61–0.74
$AUC_{0-infinity}$(ng.h/mL)	39.3–602	14700–40339

Amodiaquine in Plasmodium falciparum:

As the malaria parasite's resistance develops to existing drugs, new ones need to be introduced. For plasmodium falciparum use of two or more drugs with different modes of action in combination is now recommended to provide adequate cure rate and delay the development of resistance. Currently artemisinin-based combination therapy (ACT) is recommended for the treatment of P. falciparum malaria. Fast acting artemisinin-based compounds are combined with a drug from a different class. Companion drugs include lumefantrine, mefloquine, amodiaquine, sulfadoxine/pyrimethamine, piperaquine and chlorproguanil/dapsone.[6]

The 4-aminoquinoline amodiaquine has been used in the treatment and prophylaxis of falciparum malaria for over 40 years.

Because of rare but serious hematological and hepatic toxicity when used for malaria prophylaxis, amodiaquine is recommended only for treatment of falciparum malaria. There was a renewed interest in amodiaquine monotherapy in the face of high chloroquine resistance in the 1990s, because it was shown to retain higher efficacy than chloroquine against chloroquine-resistant parasites.[7]

In contrast to the wealth of information available about chloroquine accumulation and its relationship to activity, little is known about the uptake characteristics of amodiaquine, a drug that is inherently more active against malaria parasites. Amodiaquine accumulation in Plasmodium falciparum was shown to be 2- to 3-fold greater than chloroquine accumulation.

Study conducted by Shaun R. *et.al*. concluded that, the increased level of AQ accumulation, in comparison to that of CQ, may be due to its enhanced affinity for an intraparasitic binding site and that this subsequent increase in drug accumulation is the reason why AQ shows greater inherent activity against P. falciparum than CQ.

Development of compounds which have a greater affinity for this intraparasitic receptor could lead to enhancement of both drug accumulation and activity.[8]

5.3. PRECLINICAL SAFETY DATA

No information is available.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Polyvinylpyrollidone USP (Povidone USP)
Lactose Hydrous USP
FD&C Red No. 3 Lake Jet milled
Camoquin Base
Microcrystalline cellulose Avicel PH 101
Starch Corn NF
Magnesium Stearate

6.2. INCOMPATIBILITIES

No information is available.

6.3. SHELF LIFE

60 months

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Keep in a Cool Dry Place.
Avoid exposure to heat, light and moisture.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER

Basoquin Tablets:

Box containing 60 blisters of 10's tablet each containing amodiaquine base (P.D.) 150 mg.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

No information is available.

Basoquin/LPD/PK-02

Manufactured By:

Pfizer Pakistan Limited.
B-2, S.I.T.E., Karachi, Pakistan.

7. REFERENCES

1. Amodiaquine Hydrochloride. *NIH - U.S National Library of Medicine.* [Online] PubChem - Open Chemistry Database, Modified in August 2018. [Cited: August 7, 2018.] https://pubchem.ncbi.nlm.nih.gov/compound/517313#section=Top.

2. Pharmacology of antimalarial drugs. A5.1 Ammodiaquine. *Guidelines for the Treatment of Malaria. 3rd edition.* s.l. : Geneva: WHO Library Cataloguing-in-Publication Data, 2015, Vol. 3, 5, pp. 205-209.

3. *The disposition of amodiaquine in man after oral administration.* **P Winstanley, G Edwards, M Orme, and A Breckenridge.** 1, Jan 1987, Br J Clin Pharmacol., Vol. 23, pp. 1-7.

4. Amodiaquine. IBM Micromedex - Pharmaceutical Knowledge. [Online] April 2010. [Cited: July 23, 2018.] http://www.micromedexsolutions.com/micromedex2/librarian/CS/28D52F/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/57884D/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.Intermedi.

5. Amodiaquine Hydrochloride. *International programme on Chemical Safety.* [Online] 1993. [Cited: July 23, 2018.] http://www.inchem.org/documents/pims/pharm/amodiaqn.htm#SectionTitle:4.3%20Contraindication.

6. Artemisinin-based combination therapy. *Malaria Consortium (disease control, better health).* [Online] [Cited: August 7, 2018.] https://www.malariaconsortium.org/pages/artemisinin.htm.

7. *In Vivo and In Vitro Efficacy of Amodiaquine against Plasmodium falciparum in an Area of Continued Use of 4-Aminoquinolines in East Africa.* **Philip Sasi Abdi Abdulrahaman Leah Mwai, et.al.** 11, s.l. : Oxford Academics, June 2009, The Journal of Infectious Diseases, Vol. 199, pp. 1575-1582.

8. *Amodiaquine accumulation in Plasmodium falciparum as a possible explanation for its superior antimalarial activity over chloroquine .* **al., S.R. Hawley et.** 1996, Molecular and Biochemical Parasitology , Vol. 80, pp. 15-25.

9. NIH U.S National Library of Medicine. *TOXNET Toxicology Data Network; Amodiaquine.* [Online] 2006. [Cited: July 24, 2018.] https://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+7457.

10. *The safety of amodiaquine use in pregnant women.* **Harry K Tagbor, Daniel Chandramohan & Brian Greenwood.** 6, Ocotber 2007, Expert Opin. Drug Saf., Vol. 6, pp. 631-635.

11. *Pharmacokinetics of Amodiaquine and Desethylamodiaquine in Pregnant and Postpartum Women with Plasmodium vivax Malaria.* **Marcus J. Rijken, Rose McGready, Vincent Jullien, et.al.** 9, September 2011, ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Vol. 55, pp. 4338–4342.

12. LiverTox - Clinical & Research Information On Drug Induced Liver Injury. *NIH - National Institutes of Health.* [Online] May 7, Updated 2018. [Cited: July 23, 2018.] https://livertox.nih.gov/Amodiaquine.htm#structure.

13. *Amodiaquine induced agranulocytosis and liver damage.* **K A Neftel, et.al.** 292, s.l. : NCBI, March 15, 1986, Br Med J (Clin Res Ed), Vol. 6522, pp. 721-723.

14. Amodiaquine - Drug Information. *Med India.* [Online] [Cited: July 23, 2018.] https://www.medindia.net/doctors/drug_information/amodiaquine.htm.

15. Amodiaquine - Human Health Effects. *Toxnet - Toxicology Data Network.* [Online] Sept 2006. [Cited: August 9, 2018.] https://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+7457.

16. *Amodiaquine-lnduced Hepatitis.* **DOMINIQUE LARREY, M.D., ANNE CASTOT, M.D. and DOMINIQUE PESSAYRE, M.D et.al.** 1986, Annals of Internal Medicine., Vol. 104, pp. 801-803.