Brand Name: Krintafel®

Generic Name: Tafenoquine

Manufacturer: GlaxoSmithKline

Drug Class: Anti-malarial agent[1]

Uses:

Labeled: Radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients who are at least 16 years of age and receiving therapy for acute infection[1].

Mechanism of Action: It is unknown what tafenoquine targets molecularly. The 8-aminoquinolone antimalarial is active against pre-erythrocytic (liver) forms of *P. vivax.* The activity of tafenoquine in the liver prevents the advancement in the parasitic life cycle to the erythrocytic (asexual) forms that instigate relapses in malaria[1]. Tafenoquine also acts against asexual and gametocyte forms of the parasite including the hypnozoite (dormant stage) of *P. vivax*[2].

Pharmacokinetics:

T_{max}[1,2]	12-15 hours
V_d[1,2]	~1,600 L
$T_{1/2}$[1,2]	15 days
Clearance[1]	3 L/h
Protein Binding[1,2]	> 99.5%
Bioavailability[1]	Not reported

Metabolism: The mechanism of tafenoquine metabolism is slow and does not result in active metabolites. It has not been found to interact significantly with CYP1A2, CYP2D6, CYP2C8, CYP2C9, or CYP3A4 isoenzymes[1]. The use of MATE and OCT2 substrates with tafenoquine should be avoided due to risk of increased serum concentrations[2,3].

Elimination: Tafenoquine is excreted through unknown processes and renal elimination of unchanged drug was low over a period of six days[1].

Efficacy:

Walsh DS, Looareesuwan S, Wilairatana P, Heppner DG, Tang DB, Brewer TG, et al. Randomized Dose-Ranging Study of the Safety and Efficacy of WR 238605 (Tafenoquine) in the Prevention of Relapse of *Plasmodium vivax* Malaria in Thailand. J Infect Dis. 1999;180:1282-7 [4].

Study design: Randomized, open-label, prospective study

Description of study: *Methods:* Forty-four patients with confirmed *Plasmodium vivax* infections were randomized using a computer-generated block randomization schedule into four treatment groups, groups A through D. All patients received 1500-mg of chloroquine over three days before the treatment with tafenoquine (days -5 to -3). To continue to the next phase of treatment the patients were screened for clearance of blood parasites. If complete removal of parasitemia was achieved, the patients received tafenoquine doses on day 0 as listed: group A received 300-mg daily for 7 days, group B received 500-mg daily for 3 days and an additional 500-mg for three days one week following the initial dose, group C received 500-mg as a single dose, and group D did not receive tafenoquine. The primary efficacy outcome was the presence of *P. vivax* malaria microscopically after treatment within the 2 to 6 month follow-up period. *Outcome Results:* Patients treated with tafenoquine had a reduced incidence of annual relapse by 91% (95% CI, [39.0, 99.2]). Only one patient in groups B and C relapsed, while 4 patients relapsed in group D. The cumulative risk of relapse compared between patients on chloroquine and patients receiving tafenoquine (groups A to C) was found to be statistically significant ($P < 0.002$).

Limitations: This study consisted of a small sample size of patients specifically from Thailand that may limit generalizability. The randomization reported should have resulted in an equal number of participants across all groups, but the actual dispersion was not equivalent. The authors reported a large number of drop outs from group A during the follow-up phase that were reported as not attributable to the side effects from tafenoquine. However, the data on adverse event occurrence were not reported formally and only generalized in the results. It is hard to determine the significance of the adverse events as they were not statistically analyzed or specifically stated. The evaluations of safety after day 14 became less standardized in frequency, and were not reported across each group.

Conclusions: Tafenoquine was found to be effective in patients treated for *P. vivax* infections at several doses. However, more studies will have to be conducted to assess the safety of the drug in regards to adverse effects and most tolerable dose.

Fukuda MM, Krudsood S, Mohamed K, Green JA, Warrasak S, Noedl H, et al. A randomized, double-blind, active-control trial to evaluate the efficacy and safety of a three day course of tafenoquine monotherapy for the treatment of *Plasmodium vivax* malaria. PLOS ONE. 2017;12(11): e0187376. https://doi.org/10.137t/jornal.pone.0187376 [5].

Study design: Randomized, active-control, double-blind prospective study

Description of study: *Methods:* Seventy patients were enrolled and randomized to either tafenoquine 400-mg daily for three days or chloroquine 1000-mg daily for two days, 500-mg for one day and primaquine 15-mg daily for fourteen days following the chloroquine. All groups were given matched placebos to ensure blinding. Patients were hospitalized from day 0-28 and followed closely until discharge. The participants had scheduled follow-ups on day 60, 90, and 120 following discharge. The primary endpoint was to assess adequate clinical response by day 28 (parasitological clearance until day 28 without previous treatment failure on day 7 or late treatment failure after day 7 – 28). Secondary endpoints were the proportion of patients who did not relapse at day 60, 90, and 120, parasite clearance time, and fever clearance time. The evaluation of safety was completed by assessment of frequency and severity of adverse events and abnormal laboratory values. Safety data and secondary efficacy data were evaluated with descriptive statistics. *Outcome Results:* The 28 day adequate clinical response rate was 93% (90%

CI 83-98) in the tafenoquine group and 100% (90% CI 87-100) in the chloroquine/primaquine group. The proportion of patients who did not relapse by day 60, 90, and 120 was reported as 88% (90% CI 76-95) in the tafenoquine group and 86% (90% CI 68-96) in the chloroquine/primaquine group. The tafenoquine group required about twice as long to reach parasite clearance as compared to the chloroquine/primaquine treatment, taking a mean of 82.5 hours (SD 32.3) and 40 hours (SD 15.7) respectively. The same result was seen with time to fever clearance. Safety analyses found four serious adverse events in the tafenoquine group, all due to asymptomatic increases in methemoglobin. Other reported adverse events that were more frequent in the tafenoquine group were keratopathy and retinal disorders, upper respiratory tract infections, methemoglobinemia, headache, and dizziness.

Limitations: Two of the authors work for GlaxoSmithKline research and development team and the study was funded by GlaxoSmithKline. This creates a potential conflict of interest that may have led to bias in the study analysis and result reporting. The study did not statistically analyze the two treatment arms. The lack of statistical comparison of reported adverse effects does not allow for comparison to the active comparator either. Results of the primary efficacy measure of the chloroquine/primaquine group study were not reported in the write up, only in figure 1. This appears to be an attempt to downplay the potential benefit of traditional therapy over tafenoquine. The variance in the baseline characteristics of parasite count and time since last malarial attack between groups may have led to some differences in the reported clearance time between the groups.

Conclusions: This study confirms that tafenoquine will treat *P. vivax* infections as shown in other trials. The lack of analysis to the provided active comparator does not allow for assessment of the efficacy of tafenoquine in comparison to already available treatments. The only severe adverse events reported was the development of methemoglobinemia in the tafenoquine group. Adverse effects reported to assess the safety were not analyzed in a manner to allow comparison between the treatment groups, but they occurred more frequently in the tafenoquine treatment group.

Llanos-Cuentas A, Lacerda MV, Rueangweerayut R, Krudsood S, Gupta SK, Kochar SK, et al. Tafenoquine plus chloroquine for the treatment and relapse prevention of *Plasmodium vivax* malaria (DETECTIVE): a multicenter, double-blind, randomized, phase 2b dose-selection study. Lancet. 2014;383:1049-58 [6].

Study design: Randomized, double-blind, dose-ranging phase 2b study

Description of study: *Methods:* Three-hundred and twenty-nine patients were randomly assigned into one of six groups. All patients were given 600-mg of chloroquine for the first two days and 300-mg on day three. The study groups were given either no additional therapy or one of several possible treatments. Tafenoquine was administered as a single dose with food on day 1 or day 2 at doses of 50-mg, 100-mg, 300-mg, or 600-mg. Once daily primaquine may have also been given at 15-mg for fourteen days starting on day two. The patients were given directly observed therapy during days one to three. The patients were required to follow up on days 5, 8, 11, 15, 22, 29, 60, 90, 120, and 180 as outpatients. The primary endpoint was the proportion of patients without a relapse by 6 months. Secondary endpoints included the relapse-free efficacy at four months, time to relapse, parasite clearance time, and fever clearance time. Safety outcomes assessed were declines in hemoglobin > 25g/L or $\geq$ 25% from baseline, changes in methemoglobin, incidence and severity of adverse events, and abnormal chemistry and laboratory assessments. *Outcome Results:* The tafenoquine doses of 300-mg and 600-mg were found to have the lowest relapse rate or the highest relapse-free efficacy at 6 months with 89.2% [95% CI 77-95] and 91.9% [95% CI 80-97] respectively. Tafenoquine at the highest doses was also found to have significantly higher

efficacy compared to chloroquine treatment alone with 300-mg group difference at 51.7% [95% 35-69, p <0.0001] and the 600-mg group at 54.5% [95% CI 38-71, p <0.0001]. The relapse-free efficacy at four months was also found to be significantly higher than the chloroquine alone group in the tafenoquine 300-mg group with 42.9% [95% CI 26-60, p>0.0001] difference and 600-mg group with 51.6% [95% CI 37-66, p<0.0001] difference. No difference was found in time to parasite and fever clearance across all groups. Safety analysis found that 69% of all patients enrolled in the trial reported adverse events. Twenty-nine serious adverse events were recorded and eleven were due to asymptomatic QTc prolongation, only five of which were in the tafenoquine treatment groups. Four patients receiving tafenoquine also experienced greater than 25 g/L or at least a 25% decrease in hemoglobin and genetic analysis revealed none of these participants had G6PD variants associated with a deficiency in the enzyme.

Limitations: The funding for the study was received by the drug manufacturer, GlaxoSmithKline (GSK). GSK was also involved in the development of the study protocol, data collection, statistical analyses, and writing of the clinical report which provides a potential conflict of interest. Only 3 study sites completed ophthalmic safety assessments (Brazil, Thailand, and India). However, when results of the analysis on ophthalmic adverse effects were reported, they did not report that the number of patients with keratopathy came from the assessed populations. This may have led to biased interpretation of the clinical importance of adverse effects seen with the use of tafenoquine. The baseline characteristics reported revealed a mostly male and American Indian study sample that may limit generalizability of results. Tafenoquine was not compared to the current standard of care. This does not allow for the evaluation of the effectiveness of tafenoquine in comparison to readily available treatments.

Conclusions: Tafenoquine has utility as an agent to reduce malarial relapse in patients infected with *P. vivax.* There are significant adverse effects associated with the treatment such as decreases in hemoglobin not associated with G6PD deficiency. However, the utility of tafenoquine in comparison to already available treatments such as chloroquine/primaquine therapy is unknown and should be investigated further.

Contraindications[1,2]**:** Patients with G6PD deficiency or unknown G6PD status, breastfeeding an infant found to be G6PD deficient or of unknown status, and in patients with a known hypersensitivity to tafenoquine, components of Krintafel®, or to other 8-aminoquinolones.

Precautions:

Hemolytic Anemia[1,2,3]: G6PD testing must be performed before the use of tafenoquine due to the high risk of hemolytic anemia. Patients with G6PD deficiency or unknown G6PD status should not receive tafenoquine. Data from clinical trials excluded individuals with G6PD activity less than 70% compared to normal enzymatic activity, but declines were seen in hemoglobin even in patients with normal enzyme function. All patients should be monitored for signs and symptoms of hemolysis. A delayed reaction is possible due to the long-half-life of tafenoquine. The interaction with G6PD deficient individuals also applies to breastfeeding infants and the unborn fetus. It is recommended that women of childbearing age use adequate contraception for the duration of treatment and for three months following the dose of tafenoquine. Women who are breastfeeding should have their children tested for G6PD deficiency. If the infant's G6PD status is unknown or deficient avoid breastfeeding for three months following the dose of tafenoquine.

Hypersensitivity Reactions[1,2,3]: Serious hypersensitivity reactions such as angioedema and urticaria have been reported following the use of tafenoquine. The long half-life of the drug may lead to delayed onset or duration of the reactions. Tafenoquine should not be administered to individuals with a previous reaction, and the drug should be discontinued if a reaction does occur.

Methemoglobinemia[1,2,3]: During clinical trials the use of tafenoquine was associated with asymptomatic increases in methemoglobin. All patients should be monitored for signs and symptoms of methemoglobinemia. Patients with nicotinamide adenine dinucleotide (NADH)-dependent methemoglobin reductase deficiency should be closely monitored due to their increased risk.

Psychiatric Effects[1,2,3]: Sleep disturbances, anxiety, depression, and psychosis have been described with the use of tafenoquine. Psychosis was reported in individuals receiving doses higher than the recommended 300 mg dose and with a history of psychiatric illness. Benefits and risks of treatment should be evaluated before use in patients with medical histories significant for psychiatric illnesses. Patients should be monitored for signs and symptoms of psychiatric adverse reactions at administration and for late-onset due to the long half-life of tafenoquine.

Adverse Effects:

System	Effect	Incidence
Central Nervous System	Headache[2,3]	5-15%
	Insomnia[1,2,3]	3-4%
	Sleep disorder[2]	2-3%
	Drowsiness[2,3]	≤ 3%
	Abnormal dreams[2]	2%
	Dizziness[2,3]	1-8%
Gastrointestinal	Diarrhea[2,3]	5-18%
	Nausea[2,3]	5-7%
	Motion Sickness[2,3]	5%
	Vomiting[2,3]	5-6%
Hematologic & Oncologic	Methemoglobinemia[1,2,3]	3-13%
	Decreased hemoglobin[2,3]	2-5%
	Hemolytic anemia[1,2,3]	≤ 1%
Hepatic	Increased serum alanine aminotransferase[2,3]	3-4%
Hypersensitivity	Hypersensitivity Reactions[1,2,3]	≤ 3%
Neuromuscular & Skeletal	Back pain[2,3]	14%
Ophthalmic	Epithelial keratopathy[2,3]	3-93%
	Photophobia[2,3]	≤ 3%
Psychiatric Effects	Psychotic disorder[1,2,3]	unreported
Renal	Increased serum creatinine[2,3]	≤ 3%

Drug Interactions:

Interaction	Mechanism	Drugs Involved	
Increased plasma concentrations of interacting drug	Inhibition of MATE-mediated drug transportation	Dofetilide[2,3] Metformin[2,3]	
	Inhibition of OCT2-mediated drug transportation	Amantadine[2] Amiloride[2] Cimetidine[2] Clofarabine[2] Dopamine[2] Famotidine[2] Memantine[2]	Metformin[2,3] Oxaliplatin[2] Pindolol[2] Procainamide[2] Ranitidine[2] Varenicline[2]

Dosing/Administration:

Usual dose[1,2,3]: 300mg with Day 1 or Day 2 of antimalarial therapy such as chloroquine. Administer with a high-calorie, high-fat meal of at least 1,000 calories to increase absorption. If vomiting occurs within the first hour following administration, repeat the dose no more than once.

Use in special circumstances:

Geriatric dose[2]: Refer to usual dose.

Pediatric dose[1,2]: Only recommended in patients > 16 years of age. Refer to usual dose.

Renal and Hepatic impairment dose[2]: None recommended.

Conclusion: Tafenoquine has utility as a treatment of infections caused by *Plasmodium vivax*. The availability of a single dose treatment eliminates the concern for unfinished therapy that results in more malarial relapses. However, the advantages over currently available therapies are not known at this time. Studies with analysis of the efficacy compared to the current standard of care should be conducted. The need for G6PD deficiency gene testing may limit the usefulness of tafenoquine in areas endemic with *P. vivax* malaria due to the cost and risk of hemolytic anemia if used with unknown G6PD status. The pricing information of Krintafel® is not currently available as the marketing of the product has not begun. Due to this the cost-benefit of tafenoquine cannot be assessed at this time.

Recommended References:

(1) Krintafel [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2018.
(2) Tafenoquine. Lexi-Drugs [database online]. Lexi-comp, Inc; Accessed: October 15, 2018.
(3) Tafenoquine. In: IBM Micromedex System [database online]. Greenwood Village, Colo: Thompson Micromedex. Accessed: October 15, 2018.
(4) Walsh DS, Looareesuwan S, Wilairatana P, Heppner DG, Tang DB, Brewer TG, et al. Randomized Dose-Ranging Study of the Safety and Efficacy of WR 238605 (Tafenoquine) in the Prevention of Relapse of *Plasmodium vivax* Malaria in Thailand. J Infect Dis. 1999;180:1282-7.
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tafenoquine monotherapy for the treatment of *Plasmodium vivax* malaria. PLOS ONE. 2017;12(11): e0187376. https://doi.org/10.137t/jornal.pone.0187376.

(6) Llanos-Cuentas A, Lacerda MV, Rueangweerayut R, Krudsood S, Gupta SK, Kochar SK, et al. Tafenoquine plus chloroquine for the treatment and relapse prevention of *Plasmodium vivax* malaria (DETECTIVE): a multicenter, double-blind, randomized, phase 2b dose-selection study. Lancet. 2014;383:1049-58.

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