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Tafenoquine Therapy and *G6PD* Genotype

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Introduction

Tafenoquine is an antimalarial agent that was approved by the FDA in 2018 for (1) preventing malaria (brand name Arakoda, 100 mg tablets), and for (2) the radical cure of malaria (brand name Krintafel, 150 mg tablets) caused by Plasmodium vivax (P. vivax) (1, 2).

Malaria is caused by the Plasmodium parasite, which infects mosquitos and is spread to humans when an infected mosquito bites a person. In 2018 the World Health Organization (WHO) estimated 228 million cases of malaria occurred worldwide (3).

There are several clinical patterns of malaria that are caused by different species of the parasite. In P. vivax malaria, the parasite can lie dormant in the liver as hypnozoites, until it emerges weeks or months later, to cause a relapse of malaria. In combination with an antimalarial active against the blood stage parasites, tafenoquine provides a radical cure of P. vivax by targeting its dormant liver stage, thus preventing malaria relapse.

Tafenoquine is the second drug of its kind (with hypnozoiticidal activity) to be approved by the FDA. The first was primaquine, approved in 1952. Because of its longer half-life, tafenoquine can be dosed less frequently than primaquine, which may improve compliance. For example, when used for the radical cure of P. vivax malaria, tafenoquine is taken as a single 300 mg dose (in uncomplicated cases, in persons aged 16 years and older). In contrast, primaquine radical cure is recommended to be given daily over 14 days (4), or higher doses over 7 days (5).

Tafenoquine, like primaquine, should not be used in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. In the case of tafenoquine, an individual with <70% of normal G6PD activity is considered deficient and should not take the drug (6).Worldwide, approximately 400 million people have a deficiency of the G6PD enzyme, but most are asymptomatic and do not know they are at risk (7). A lack of G6PD in red blood cells makes the cells susceptible to damage by oxidative stress. Usually, only low levels of oxidative stress occur naturally, and so the condition is undetected.

However, certain drugs, which include tafenoquine and primaquine, are oxidizing agents. In people with G6PD deficiency, these drugs cause irreparable oxidative damage to the red blood cells, which are then rapidly destroyed (hemolysis). This can lead to a potentially life-threatening deficiency of mature red blood cells (hemolytic anemia).

The FDA-approved drug label for tafenoquine states that testing for G6PD must be performed before starting tafenoquine therapy, and that all individuals should be monitored for signs of hemolysis (Table 1). In addition,

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because of the risk of tafenoquine causing fetal harm in a woman pregnant with a fetus with G6PD deficiency, pregnancy testing is highly recommended in women of reproductive age. Consequently, tafenoquine therapy is contraindicated in adults when the G6PD status is either unknown, intermediate or deficient, namely, enzyme activity lower than 70%, in pregnancy, and in breastfeeding mothers when the infant's G6PD status is either unknown or deficient (1). To date, no safety studies have been reported in children.

Table 1. The FDA Drug Label for Tafenoquine (Arakoda). Contraindicated in G6PD Deficiency. (2019)

Phenotype	Warnings and precautions
G6PD deficiency	Hemolytic Anemia: G6PD testing must be performed before prescribing tafenoquine due to the risk of hemolytic anemia. Monitor individuals for signs or symptoms of hemolysis. G6PD Deficiency in Pregnancy or Lactation: tafenoquine may cause fetal harm when administered to a pregnant woman with a G6PD-deficient fetus. Tafenoquine is not recommended during pregnancy. A G6PD-deficient infant may be at risk for hemolytic anemia from exposure to tafenoquine through breast milk. Check infant's G6PD status before breastfeeding begins.

G6PD: Glucose-6-phosphate dehydrogenase
This FDA table is adapted from (1).

Disease: Malaria

Malaria is a serious tropical disease caused by a parasite (*Plasmodium*) that spreads to humans by infected mosquitos. The only available vaccine is moderately effective and acts only against *Plasmodium falciparum (P. falciparum)* species (8). Widely recommended antimalarial drugs such as tafenoquine can be used for prevention –– this is known as chemoprophylaxis. The type of chemoprophylaxis recommended depends upon the individual taking the prophylaxis (namely, age, pregnancy status, and medical comorbidities) and the nature of travel –– specifically, the countries travelled to, the length of stay, the species of Plasmodium that are most prevalent, and the level of drug resistance.

Despite chemoprophylaxis, travel to malaria-endemic areas is not without risk. Individuals at elevated risk for malaria complications include pregnant women (9) and adults who have had their spleen removed (10). If travel cannot be avoided, chemoprophylaxis should be combined with additional precautions to avoid mosquito bites, such as bed nets and repellents. In 2018, the WHO estimated 228 million cases of malaria occurred worldwide, and malaria was responsible for 405,000 deaths. (3)

Malaria is found in over 100 countries and occurs throughout most tropical regions in the world. These regions include large parts of Africa, Asia, Central and South America, and parts of the Middle East and Pacific islands (3, 11). Individuals who are heterozygous carriers for sickle cell disease and G6PD deficiency have a protective advantage against malaria, and as a result, the frequency of such genetic conditions is higher in countries where malaria is endemic (12).

Malaria is transmitted to humans by the bite of an infected *Anopheles* mosquito. Only female mosquitos spread the infection (females feed on human blood, males feed on nectar). Although malaria can also be spread by sharing contaminated needles or via a contaminated blood transfusion, these are rare means of transmission.

There are several different Plasmodium species, but only a few species cause the most malaria cases:

- *P. falciparum*
  - The most common cause of malaria, and death from malaria
  - Predominates in sub-Saharan Africa
  - Also found in regions of Australasia (Papua New Guinea, Southeast Asia), and the Caribbean (Haiti and the Dominican Republic)
- *P. vivax*
  - A common cause of malaria outside of Africa

    - Most frequent species found in Central and South America
    - Parasite has a dormant, hypnozoite stage
    - Early gametocytes that infect mosquitos
- *P. malariae*
    - Less common
    - Found in most areas where malaria is endemic
- *P. ovale*
    - Less common
    - Parasite has a dormant, hypnozoite stage
- *P. knowlesi*
    - Less common
    - Found in some Southeast Asia areas

The first stage of malaria infection begins when an infected mosquito bites the human host. Typically, mosquitos bite at dusk, or during the night. As the mosquito feeds, infective parasite sporozoites (the motile spore-like stage in the life cycle of this parasitic sporozoan, which is the infective agent) are inoculated into humans. The sporozoites travel to the liver, where they invade liver cells and asexually reproduce to form schizonts. The liver schizonts contain daughter merozoites. This process is asymptomatic, and because it occurs outside of the red blood cell (erythrocyte), it is known as the exoerythrocytic stage.

Some species of the parasite (*P. vivax* and *P. ovale*) have an additional dormant stage in the liver. The parasite exists as hypnozoites, which can stay in the liver for weeks or months without causing any clinical symptoms.

The second stage of malaria infection is the erythrocytic stage. It begins when the liver schizonts rupture and release the daughter merozoites into the bloodstream. The merozoites invade red blood cells, digest hemoglobin, produce a toxic metabolite (hemozoin), and damage red blood cell membranes. Infected, brittle red blood cells are rapidly broken down (hemolysis) and if too many damaged red blood cells get trapped in the spleen, the spleen can rapidly enlarge (splenic sequestration).

Some of the daughter merozoites differentiate into male or female gametocytes (sexual forms). When they are ingested by a mosquito, they mature, fertilize and reproduce, and develop into sporozoites. When the mosquito feeds again, the sporozoites are inoculated into another human host and the cycle of malaria transmission is complete.

The erythrocytic stage of malaria is usually associated with fever, and malaria should always be suspected in anyone with a fever who has recently returned from a malaria-endemic region, even if antimalarial chemoprophylaxis was correctly followed. Other symptoms and signs include nausea, vomiting, abdominal pain, tachycardia (fast heart rate), diaphoresis (sweating), chills, and myalgia (muscle pain).

The complications of malaria infection include severe anemia, cerebral malaria, and multi-organ failure. Without correct diagnosis and prompt treatment, malaria can be fatal.

Drug: Tafenoquine

Malaria drugs can be used to prevent malaria as primary prophylaxis, to prevent infection (started before travel to a country where malaria is endemic) or as terminal prophylaxis to prevent a relapse of malaria (started after returning home from prolonged travels in malaria-endemic regions) (13).

Tafenoquine is one of 2 antimalarials, the other is primaquine, that is used both for primary prophylaxis and radical cure of malaria. Specifically, tafenoquine is approved by the FDA for 2 indications:

- Prophylaxis of malaria, in adults (Arakoda, 100 mg tablets) (11, 14).
- Radical cure of *P. vivax* malaria, in persons aged 16 years and older (Krintafel, 150 mg tablets) (2).

The "radical cure" of *P. vivax* malaria refers to the complete elimination of the malaria parasite from the body. Specifically, the elimination of both parasites in the blood and parasites that are lying dormant in the liver, known as hypnozoites, which can cause malaria relapse weeks or months after travel. This occurs in malaria caused by *P. vivax* (a common cause of malaria) and *P. ovale* (a less common cause).

Tafenoquine is the most recent addition to the drug family of 8-aminoquinoline antimalarials, which only includes one other actively prescribed drug: primaquine. Both drugs provide malaria prophylaxis, and both drugs can prevent relapse of *P. vivax* malaria. However, tafenoquine has a longer half-life, allowing for less frequent dosing (13, 15-17).

For prophylaxis against all species of malaria, treatment with tafenoquine (Arakoda) is started just 3 days before travel (loading regimen of 200 mg once daily for 3 days). Tafenoquine is then taken once a week while traveling in the malaria-endemic area (maintenance regimen of 200 mg once weekly, starting 7 days after the last loading dose), with one final dose taken after returning home, away from the malaria-endemic area (terminal prophylaxis regimen of 200 mg once, 7 days after the last maintenance dose) (1).

For the radical cure of *P. vivax* malaria, tafenoquine (Krintafel) is taken as a single 300 mg dose in conjunction with a blood schizontocidal antimalarial. Previously, the best available treatment for radical cure of *P.vivax* was a 14-day course of primaquine, (2) although 7-day courses are used in some countries (5).

Tafenoquine is active against the different forms of the malaria parasite: the pre-erythrocytic (liver stage), the erythrocytic (red blood cell, asexual form) stage, and the gametocytes (sexual form). By targeting the pre-erythrocytic stage, tafenoquine prevents the parasite from developing erythrocytic forms and halts progression of the disease. Although the molecular target of tafenoquine is not known, in vitro studies suggest that the drug may inhibit hematin polymerization, which kills the parasite, and also causes red blood cells to shrink (13, 17). It is also thought that tafenoquine has many different metabolites to target the different stages of the parasites (18).

Before starting tafenoquine therapy, all adults must be tested for G6PD deficiency. Individuals with G6PD deficiency have red blood cells that are susceptible to oxidative damage. If exposed to oxidizing agents such as tafenoquine or primaquine, the red blood cells become rigid, get trapped, and are subsequently destroyed by macrophages in the spleen, bone marrow, and liver. The rapid destruction of red blood cells is called hemolysis, and it may result in hemolytic anemia (low number of red blood cells due to increased hemolysis without sufficient production of new cells).

The degree of G6PD activity can vary based on the allele(s) present in the individual. Individuals with a partial decrease in G6PD function are still susceptible to hemolysis while taking 8-aminoquinoline antimalarial drugs. Primaquine can be prescribed for individuals with at least 30% of the normal levels of G6PD enzyme activity. Individuals with intermediate (30–70%) levels of activity should be monitored for hemolysis. Tafenoquine, however, should not be given to individuals with less than 70% of the normal G6PD enzymatic activity. (6)

Pregnancy testing is also recommended for women of reproductive age, because tafenoquine may cause fetal harm when given to a woman who is pregnant with a G6PD-deficient fetus. Therefore, the FDA does not recommend tafenoquine therapy during pregnancy. Tafenoquine is also contraindicated during breastfeeding when the infant is G6PD deficient or if the G6PD status of the infant is unknown.

One study found that in women with normal (>80%) G6PD enzymatic activity, tafenoquine and primaquine resulted in a similar decline in hemoglobin (19, 20). The impact of such 8-aminoquinolines is not clear in individuals with intermediate enzyme activity (30–80%). Usually primaquine is not recommended for those presenting with activity under 30%. Tafenoquine clinical studies were safe in individuals with more than 70% of activity.

Adverse reactions to tafenoquine include hemolytic anemia, as discussed above, in addition to methemoglobinemia (elevations in methemoglobin that require careful monitoring of individuals with NADH-

dependent methemoglobin reductase deficiency); uncommon psychiatric effects (including anxiety, abnormal dreams, and insomnia); and serious hypersensitivity reactions (including angioedema and urticaria –– tafenoquine therapy should stop and not be re-administered). Due to the long half-life of tafenoquine (approximately 13–19 days), signs or symptoms of psychiatric and hypersensitivity adverse reactions that may occur could be delayed in onset, duration, or both, so individuals should be advised to seek medical attention if symptoms occur.

Gene: *G6PD*

The G6PD enzyme is encoded by the *G6PD* gene, which is located on chromosome Xq28. As such, males are hemizygous for one *G6PD* allele, making them more susceptible to this X-linked disorder. Females randomly inactivate one X chromosome during development, resulting in a mosaic expression of either one X chromosome or the other in their somatic cells. This mosaicism can occur in the hematopoietic progenitor cells that give rise to red blood cells, resulting in mixed expression of *G6PD* alleles. Females with Turner syndrome (45,X) have only one X chromosome and thus are also hemizygous for the *G6PD* gene.

Glucose-6-phosphate dehydrogenase deficiency affects 400 million people worldwide (7), with a worldwide prevalence of approximately 5%. Glucose-6-phosphate dehydrogenase deficiency appears to be protective against malaria infection leading to a higher prevalence (more than 25%) in countries where malaria is, or once was, endemic for example,, tropical Africa, tropical and subtropical Asia, the Middle East, and some parts of the Mediterranean (21-23). In the US, G6PD deficiency is more common among African-Americans, affecting approximately 12% (24).

The G6PD enzyme catalyzes the first step in the hexose monophosphate shunt (HMP) pathway, which converts glucose to pentose sugars for nucleic acid synthesis. In this step nicotinamide adenine dinucleotide phosphate (NADP+) is reduced to NADPH, which protects cells from oxidative stress. In mature red blood cells, the HMP pathway is the only source of NADPH. This promotes the generation of reduced glutathione that protects the sulfhydryl groups of hemoglobin, which are susceptible to oxidation by hydrogen peroxide and oxygen radicals. Red blood cells that lack G6PD also have a deficiency of NADPH. (25)

Red blood cells that are G6PD and NADPH deficient are more susceptible to oxidative stress (for example, by reactive oxygen species and hydrogen peroxide). Oxidative stress occurs naturally, but is increased during illnesses, such as infections and diabetic ketoacidosis. Oxidative stress can also follow the ingestion of fresh fava beans (favism), and is an adverse effect of several drugs, for example, the antimalarial drugs primaquine and tafenoquine, the antibacterials dapsone and sulfamethoxazole, the skin cancer drug dabrafenib, and the uric acid lowering drugs pegloticase and rasburicase.

Most individuals with G6PD deficiency are asymptomatic –– they have a normal lifespan and may not know they have G6PD deficiency. However, at birth, they maybe predisposed to neonatal jaundice, and throughout life, they will be sensitive to oxidizing agents. All individuals with G6PD deficiency should avoid exposure to oxidizing agents when possible, including drugs such as tafenoquine.

Symptomatic individuals with G6PD deficiency may suffer from episodes of acute hemolytic anemia or chronic non-spherocytic hemolytic anemia. The management of hemolytic episodes depends on the severity of hemolysis, with more severe cases requiring blood transfusions. Folic acid may be given to prevent the worsening of anemia in individuals with folate deficiency and to induce formation of new red blood cells.

More than 180 genetic variants of the *G6PD* gene have been identified so far, with approximately 400 biochemical and enzyme variants (26). Most known *G6PD* variants are missense, which can also be inherited as haplotypes that are comprised of more than one variant allele (27). Large deletions are rare, and a complete lack of G6PD activity is thought to be fatal in utero.

The normal (wild-type) copy of the *G6PD* gene is known as *G6PD* B, and is found in most Caucasians, Asians, and most Africans. Common *G6PD* variants include:

- *G6PD* A+ (p.Asn126Asp) has normal enzyme activity and is not associated with hemolysis, and is found in up to 30% of Blacks from Africa (28)
- *G6PD* A- (p.Asn126Asp with p.Val68Met) is associated with mild to moderate hemolysis, and is found in up to 15% of African-Americans (29). Additional *A-* haplotypes have also been identified, both with the A+ variant with a second SNP (p.Asn126Asp with p.Arg227Leu; and p.Asn126Asp with p.Leu323Pro. See Nomenclature table below for additional information) (30)
- *G6PD* Mediterranean (p.Ser218Phe) can cause severe hemolysis, and is a common pathogenic variant in Caucasians (31)
- *G6PD* Canton (p.Arg489Leu) can cause severe hemolysis, and is found in Asians (32)

The WHO categorized *G6PD* variants into 5 classes according to the level of enzyme activity and severity of hemolysis. Class 1 variants are the most severe, but rare. These variants have less than 10% of normal GP6D enzyme activity—often as low as 1% or less—and are associated with chronic hemolytic anemia.

Most individuals with G6PD deficiency have variants that belong to class II (enzyme activity less than 10% but no chronic hemolytic anemia) and class III (enzyme activity between 10% and 60%). Class II and III variants are associated with intermittent hemolysis, usually triggered by infection or drugs, but most of the time, affected individuals are asymptomatic. Class IV and V variants are not considered to be clinically significant, class IV variants are associated with normal enzyme activity, and class V variants with increased enzyme activity (33).

The Clinical Pharmacogenetics Implementation Consortium (CPIC) has assigned *G6PD* phenotypes based on *G6PD* genotypes (Table 2) (33).

Table 2. Assignment of likely *G6PD* Phenotype based on Genotype/Diplotype (CPIC 2014)

Likely phenotype	Definition	Genotype	WHO class for *G6PD* variants[a]	Example of diplotype[b]
Normal	Very mild or no enzyme deficiency (less than 60% of normal enzyme levels)	A male who has a nondeficient (class IV) allele	IV	B, Sao Boria
		A female who has 2 nondeficient (class IV) alleles	IV/IV	B/B, B/Sao Boria
Deficient	Less than 10–60% of normal enzyme activity	A male who has a deficient (class II–III) allele	II, III	A–, Orissa, Kalyan-Kerala, Mediterranean, Canton, Chatham
		A female who has 2 deficient (class II–III variants) alleles	II/II, II/III, III/III	A–/A–, A–/Orissa, Orissa/Kalyan-Kerala, Mediterranean/Mediterranean, Chatham/Mediterranean, Canton/Viangchan
Deficient with CNSHA	Severe enzyme deficiency (<10% activity) and associated with CNHSA	A male who has a class I allele	I	Bangkok, Villeurbanne
		A female who has 2 deficient (class I variants) alleles	I/I	Bangkok/Bangkok, Bangkok/Villeurbanne

Table 2. continued from previous page.

Likely phenotype	Definition	Genotype	WHO class for *G6PD* variants[a]	Example of diplotype[b]
Variable[c]	Normal or deficient enzyme activity[c]	A female who has one nondeficient (class IV) and one deficient (class I–III variants) allele	IV/I, IV/II, IV/III	B/A–, B/Mediterranean, B/Bangkok

CNSHA, chronic nonspherocytic hemolytic anemia
WHO, World Health Organization
[a] WHO classifications (from ref. 14, other details from ref. 17, from (33)). Class I variants are extremely rare; the distinction between class II and III variants is not clear, and the "class V" very high activity variant has been reported in only a single case. Therefore, almost all individuals will have class II, III, or IV alleles. It should be noted that the class of a variant may have been assigned only by the clinical manifestations of an individual in which the variant was subsequently identified.
[b] Due to the large number of G6PD variants, many other diplotypes may be possible besides those given as examples here; see Supplementary Table S1 online for a more comprehensive list of variant alleles with their assigned WHO class (33). For HGVS terms, please see the Nomenclature table below.
[c] Due to X-linked mosaicism, females heterozygous for one nondeficient (class IV) and one deficient (class I–III variants) allele may display a normal or a deficient phenotype. It is therefore difficult to predict the phenotype of these individuals (Supplementary Material online (G6PD heterozygotes)) (33).
This CPIC table is adapted from (33).

Linking Gene Variation with Treatment Response

Tafenoquine is contraindicated in individuals with G6PD deficiency, and published drug trials have only included adults with normal (>70%) G6PD activity. However, one study reported that 2 females with G6PD deficiency were mistakenly diagnosed as having normal G6PD activity and given tafenoquine. Both females were positive for the (A-) *G6PD* variant. While the female who was homozygous for this variant remained asymptomatic, the female who was heterozygous for this variant required a blood transfusion, emphasizing the importance of accurate G6PD testing (34, 35).

Genetic Testing

The NIH Genetic Testing Registry, GTR, displays genetic tests that are available for tafenoquine response and the *G6PD* gene. Molecular genetic testing can be used to confirm the diagnosis of G6PD deficiency and testing may also be used to screen females with a family history of G6PD to see if they are carriers.

Glucose-6-phosphate dehydrogenase deficiency is inherited in an X-linked recessive pattern and most individuals are asymptomatic throughout life.

X-linked disorders affect males at a much higher rate than females because males only have one copy of the X chromosome (hemizygous, XY). Since females have 2 copies of the X chromosome (XX) they tend to be less affected. However, female carriers can present with a range of phenotypes from no symptoms through a severe deficiency due to the high frequency of *G6PD* variants. Females randomly inactivate one X chromosome in somatic cells during development, resulting in a mixed population of somatic cells expressing one *G6PD* allele or the other.

Glucose-6-phosphate dehydrogenase deficiency occurs in homozygous and compound heterozygous females (who have inherited 2 copies of *G6PD* deficiency alleles) and in heterozygous females (one normal *G6PD* allele and one deficiency *G6PD* allele) with skewed X-chromosome inactivation of the functional allele (22). Genetic testing alone is insufficient for heterozygous females with one normal function *G6PD* allele, as the expression of the 2 alleles will vary between blood cells and over time (33).

A heterozygous mother has a 50% chance of passing G6PD deficiency to a son and a 50% chance of passing the carrier trait to a daughter. Affected fathers pass the variant *G6PD* to their daughters, but not to their sons.

The FDA recommends that all adults be tested for G6PD deficiency before starting tafenoquine therapy. In routine clinical practice, G6PD deficiency is diagnosed by measuring G6PD activity in red blood cells. Two different types of enzyme activity tests are used: qualitative and quantitative. Often, qualitative tests do not accurately detect individuals with intermediate G6PD activity, hence the importance of the quantitative enzyme assay before initiating tafenoquine therapy (6). False results may be obtained immediately after a blood transfusion, because transfused cells are likely to have normal G6PD levels, and immediately after an episode of hemolysis, because young red blood cells have higher levels of G6PD. Therefore, screening for G6PD should be performed 2–3 months after a blood transfusion or hemolytic episode. Note, false negatives have been reported (25, 33, 36).

In men, if genetic testing determined that an individual was G6PD deficient, the use of tafenoquine would be contraindicated. However, a negative genetic testing result cannot be entirely relied upon because only a small subset of *G6PD* variants are routinely tested for. In addition, the *G6PD* phenotype may be unpredictable in heterozygous females because of random X-chromosome inactivation.

The WHO recommends that neonatal screening be performed in areas where G6PD deficiency occurs in more than 3–5% of males (22). These populations are primarily in Asia, Africa, along the Mediterranean and in the Middle East. Screening either uses quantitative enzyme activity assays, or the WHO-approved fluorescent spot test –– a qualitative test that visually identifies NADPH, which is produced by G6PD (if the blood spot does not fluoresce, the test is positive for G6PD deficiency) (33, 37). However, a negative fluorescent spot test does not mean the G6PD activity level is within safe limits for tafenoquine therapy, this must be ascertained with a quantitative test.

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2018 Statement from the US Food and Drug Administration (FDA) for tafenoquine (Krintafel):

Hemolytic Anemia

Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing must be performed before prescribing tafenoquine. Due to the limitations with G6PD tests, physicians need to be aware of residual risk of hemolysis and adequate medical support and follow-up to manage hemolytic risk should be available. Treatment with tafenoquine is contraindicated in patients with G6PD deficiency or unknown G6PD status. In clinical trials, declines in hemoglobin levels were reported in some G6PD-normal patients. Monitor patients for clinical signs or symptoms of hemolysis. Advise patients to discontinue tafenoquine and seek medical attention if signs of hemolysis occur.

G6PD Deficiency in Pregnancy and Lactation

Potential Harm to the Fetus

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug. Certain terms, genes and genetic variants may be corrected in accordance to nomenclature standards, where necessary. We have given the full name of abbreviations, shown in square brackets, where necessary.

The use of tafenoquine during pregnancy may cause hemolytic anemia in a G6PD-deficient fetus. Even if a pregnant woman has normal levels of G6PD, the fetus could be G6PD deficient. Advise females of reproductive potential that treatment with tafenoquine during pregnancy is not recommended and to avoid pregnancy or use effective contraception during treatment and for 3 months after the last dose of tafenoquine. If a pregnancy is detected during tafenoquine use, discontinue tafenoquine as soon as possible and switch to an alternative prophylactic drug for malaria during pregnancy.

Potential Harm to the Breastfeeding Infant

A G6PD-deficient infant may be at risk for hemolytic anemia from exposure to tafenoquine through breast milk. Infant G6PD status should be checked before breastfeeding begins. Tafenoquine is contraindicated in breastfeeding women when the infant is found to be G6PD deficient or the G6PD status of the infant is unknown. Advise the woman with a G6PD-deficient infant or if the G6PD status of the infant is unknown not to breastfeed during treatment with tafenoquine and for 3 months after the final dose.

Methemoglobinemia

Asymptomatic elevations in methemoglobin have been observed in the clinical trials of tafenoquine. Institute appropriate therapy if signs or symptoms of methemoglobinemia occur. Carefully monitor individuals with nicotinamide adenine dinucleotide (NADH)-dependent methemoglobin reductase deficiency. Advise patients to discontinue tafenoquine and seek medical attention if signs of methemoglobinemia occur.

Please review the complete therapeutic recommendations that are located here: (2).

Nomenclature for Selected *G6PD* Variants

Common allele name / condition	Alternative names / condition	HGVS reference sequence		WHO Classification*	dbSNP reference identifier for allele location
		Coding	Protein		
G6PD B	WT	NM_001042351.3	NP_001035810.1	IV/ Normal	--
G6PD A+	p.Asn126Asp	NM_001042351.3 :c.376A>G	NP_001035810.1:p.Asn126Asp	IV/ Normal	rs1050828
G6PD Sao Boria	p.Asp113Asn	NM_001042351.3:c.337G>A	NP_001035810.1:p.Asp113Asn	IV/ Normal	rs5030870
G6PD A-	A-$^{202A/376G}$	NM_001042351.3 :c.376A>G	NP_001035810.1:p.Asn126Asp	III/ Deficient	rs1050828 rs1050829
		NM_001042351.3:c.202G>A	NP_001035810.1:p.Val68Met		
G6PD A-	A-$^{680T/376G}$	NM_001042351.3 :c.376A>G	NP_001035810.1:p.Asn126Asp	III/ Deficient	rs1050828 rs137852328
		NM_001042351.3: c.680G>T	NP_001035810.1:p.Arg227Leu		
G6PD A-	A-$^{968C/376G}$	NM_001042351.3 :c.376A>G	NP_001035810.1:p.Asn126Asp	III/ Deficient	rs1050828 rs76723693
		NM_001042351.3:c.968T>C	NP_001035810.1:p.Leu323Pro		
G6PD Bangkok	p.Lys275Asn	NM_001042351.3:c.202G>A	NP_001035810.1:p.Val68Met	III/ Deficient	
G6PD Kalyan-Kerala	p.Glu317Lys	NM_001042351.3:c.949G>A	NP_001035810.1:p.Glu317Lys	III/ Deficient	rs137852339
G6PD Orissa	p.Ala44Gly	NM_001042351.3:c.131C>G	NP_001035810.1:p.Ala44Gly	III/ Deficient	rs78478128
GP6D Canton	p.Arg459Leu	NM_001042351.3: c.1376G>T	NP_001035810.1:p.Arg459Leu	II/ Deficient	rs72554665
G6PD Chatham	p.Ala335Thr	NM_001042351.3:c.1003G>A	NP_001035810.1:p.Ala335Thr	II/ Deficient	rs5030869

Table continued from previous page.

Common allele name / condition	Alternative names / condition	HGVS reference sequence		WHO Classification*	dbSNP reference identifier for allele location
		Coding	Protein		
G6PD Mediterranean	p.Ser188Phe	NM_001042351.3:c.563C>T	NP_001035810.1:pSer188Phe	II/ Deficient	rs5030868
G6PD Viangchan	p.Val291Met	NM_001042351.3:c.871G>A	NP_001035810.1:p.Val291Met	II/ Deficient	rs137852327
G6PD Villeurbanne	p.Thr334del	NM_001042351.3:c.1000_1002delACC	NP_001035810.1:pThr334del	I/Deficient with CNSHA	

Additional allele information available from PharmGKB and CPIC's G6PD Allele Definition Table (revised 2018).
Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).
* WHO classifications based on (38)

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