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Rasburicase Therapy and *G6PD* and *CYB5R* Genotype

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Introduction

Rasburicase (brand name Elitek) is a uric oxidase used to treat the high levels of uric acid that are associated with tumor lysis syndrome (TLS).

Tumor lysis syndrome is a potentially life-threatening condition caused by rapid break down of tumor cells during chemotherapy. Tumor lysis syndrome is associated with the treatment of aggressive lymphoma and leukemia, but it may also occur with other tumors including solid tumors. Massive cell breakdown results in the release of potassium, phosphate, and uric acid into the circulation. Urate crystals can precipitate in the kidneys, causing acute kidney damage.

Prophylaxis and treatment of TLS involve aggressive intravenous (IV) hydration and the use of drugs to lower uric acid levels. Rasburicase breaks down uric acid to a more soluble metabolite (allantoin), which is then eliminated by the kidneys. A by-product of this reaction is hydrogen peroxide, an oxidizing agent.

Red blood cells that lack the enzyme glucose-6-phosphate dehydrogenase (G6PD) are sensitive to oxidative damage caused by agents like hydrogen peroxide due to a deficiency in nicotinamide adenine dinucleotide phosphate (NADPH). Once exposed, the red blood cells become rigid, trapped, and are rapidly broken down (hemolysis). This can lead to a deficiency of mature red blood cells (hemolytic anemia) and the production of red blood cells with abnormally high levels of methemoglobin (methemoglobinemia).

Approximately 400 million people worldwide have G6PD deficiency. Most of these individuals are asymptomatic. However, they are at risk of life-threating hemolytic reactions and methemoglobinemia if given oxidizing drugs such as rasburicase.

Rasburicase is contraindicated in individuals with G6PD deficiency. The FDA-approved drug label states that individuals at higher risk for G6PD deficiency should be screened before starting rasburicase therapy, for example, individuals of African or Mediterranean ancestry (Table 1) (1). Approximately 12% of African-Americans have G6PD deficiency.

A rare cause of methemoglobinemia is a deficiency of antioxidant enzymes such as cytochrome b5 reductase 3 (CYB5R3). The drug label states it is not known whether individuals who have a deficiency of this enzyme, or another enzyme with antioxidant activity, are at increased risk of methemoglobinemia or hemolytic anemia during rasburicase therapy.

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The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published dosing recommendations for rasburicase based on *G6PD* phenotype (Table 2). The CPIC states for individuals with normal *G6PD* phenotype, there is no reason to withhold rasburicase based on G6PD status. For individuals who are G6PD deficient, with or without hemolytic anemia, rasburicase is contraindicated. For individuals who have a variable *G6PD* phenotype, G6PD enzyme activity must be measured to ascertain that G6PD status is normal. For cases where rasburicase is contraindicated, alternative drugs include allopurinol (2).

Table 1. FDA Drug Label for Rasburicase. Contraindicated in G6PD Deficiency (2019)

Phenotype	Recommendations
G6PD deficiency	Do not administer rasburicase to individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Immediately and permanently discontinue rasburicase in individuals developing hemolysis. Screen individuals at higher risk for G6PD deficiency (for example, individuals of African or Mediterranean ancestry) before starting rasburicase

This table is adapted from (1).

Table 2. CPIC Recommended Therapeutic Use of Rasburicase in relation to G6PD Phenotype (2014)

G6PD phenotype	Implications for phenotypic measures	Dosing recommendations for rasburicase	Classification of recommendations[a]
Normal[b]	Low or reduced risk of hemolytic anemia	No reason to withhold rasburicase based on G6PD status[b]	Strong
Deficient or deficient with CNSHA	At risk of acute hemolytic anemia	Rasburicase is contraindicated; alternatives include allopurinol[c]	Strong
Variable[b]	Unknown risk of hemolytic anemia	To ascertain that G6PD status is normal, enzyme activity must be measured; alternatives include allopurinol[c]	Moderate

CNSHA, chronic nonspherocytic hemolytic anemia
[a] Rating scheme described in Supplementary Material online (see Strength of Recommendations, (2)).
[b] A negative or inconclusive genetic test cannot be assumed to indicate normal G6PD phenotype; an enzyme activity test is needed to assign G6PD phenotype in such cases.
[c] Allopurinol is associated with severe cutaneous reactions in the rare carriers of the HLA-B*58:01 allele.
This table is adapted from (2).

Drug: Rasburicase

Rasburicase is a urate-lowering drug used to prevent and manage TLS. In individuals with cancers such as acute leukemia and lymphoma, chemotherapy can lead to massive break down of cells, which releases large amounts of potassium, phosphate, and nucleic acids into the circulation. The purines found in nucleic acids are broken down to uric acid, which leads to hyperuricemia (uric acid levels above 6.8 mg/dL).

Tumor lysis syndrome is potentially life threatening – hemorrhage may occur, and acute kidney damage can be caused by the precipitation of urate crystals within the kidney tubules. The management of TLS is centered on prevention, with aggressive IV hydration and the use of hypouricemic agents such as allopurinol and rasburicase.

The tumors that have the highest risk of TLS are acute lymphoblastic leukemia and aggressive lymphomas, especially Burkitt's lymphoma. But TLS can also occur in other tumors including solid tumors –– risk factors include a high tumor burden, a high proliferative rate, and a high sensitivity to chemotherapy (3).

Rasburicase is a uric acid oxidase (uricase). It converts uric acid to allantoin – a metabolite that is 5–10 times more soluble than uric acid, which can be excreted by the kidneys. The uricase enzyme is present in many mammals, but absent in humans. Rasburicase is a recombinant protein derived from a genetically modified

strain of yeast (*Saccharomyces cerevisiae*). Pegloticase is another uricase that is used to manage gout, and is derived from the uricase found in pigs.

Rasburicase is given by an IV infusion, daily, for up to 5 days. Dosing beyond 5 days, or giving more than one course, is not recommended. Recent studies have found that conservative treatment with rasburicase is as beneficial, with a single dose of rasburicase being sufficient to normalize the uric acid levels in most individuals with TLS (4-6).

Rasburicase may cause fetal harm and should only be used during pregnancy if the potential benefit to the mother justifies the potential risk to the fetus. There are no adequate studies in pregnant women, but in animal studies, rasburicase was shown to be teratogenic (caused abnormal development in rabbit embryos). (1)

The use of rasburicase is contraindicated in individuals known to have G6PD deficiency, and individuals at risk of G6PD deficiency should be screened before starting rasburicase therapy. This is because an oxidizing agent, hydrogen peroxide, is produced during the conversion of uric acid to allantoin.

Individuals who have G6PD deficiency have red blood cells that are susceptible to oxidative damage. If exposed to agents such as hydrogen peroxide, 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 (a deficiency of red blood cells or hemoglobin, caused by hemolysis).

In addition, rasburicase can result in methemoglobinemia –– the production of red blood cells with abnormally high levels of oxidised hemoglobin, namely, methemoglobin. Individuals who may be at increased risk of methemoglobinemia include individuals with a rare hereditary form of methemoglobinemia. This condition may be asymptomatic, and only become apparent after an adverse reaction to an oxidizing drug such as rasburicase (1).

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%. This 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 (8-10). In the US, G6PD deficiency is more common among African-Americans, affecting approximately 12% (11).

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 sulphydryl 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(12).

Red blood cells that are G6PD and NADPH deficient are more susceptible to oxidative stress (for example, by oxygen free radicals 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 uric acid lowering drugs pegloticase and rasburicase, the antimalarial drug primaquine, the antibiotic sulfamethoxazole, and the skin cancer drug dabrafenib.

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

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 (13). Most genetic variations are missense point variants (14). 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 Blacks. 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 (15)
- *G6PD* A- (p.Asn126Asp and p.Val68Met) is associated with mild to moderate hemolysis, and is found in up to 15% of African-Americans (16). 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) (17)
- *G6PD* Mediterranean (p.Ser218Phe) can cause severe hemolysis, and is the most common abnormal variant in Caucasians (18)
- *G6PD* Canton (p.Arg489Leu) can cause severe hemolysis, and is found in Asians (19)

The World Health Organization 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 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 for most of the time, affected individuals have no symptoms. 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 (2).

The Clinical Pharmacogenetics Implementation Consortium (CPIC) assign G6PD phenotype based on *G6PD* genotype (Table 3) (2).

Table 3. 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

Table 3. continued from previous page.

Likely phenotype	Definition	Genotype	WHO class for G6PD variants[a]	Example of diplotype[b]
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
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 (2)). 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 (2).
[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)) (2).
This table is adapted from (2).

Gene: *CYB5R3*

The cytochrome b5 reductases (CYB5R family, formerly known as methemoglobin reductases) are a family of flavoproteins that catalyze reduction reactions by using NADH. In humans, there are 4 members of this family (CYB5R1-4), and they are involved in several metabolic reactions, including the formation and breakdown of fatty acids, cholesterol synthesis, and the metabolism of drugs (20).

One important reaction primarily catalyzed by CYB5R3 is the reduction of methemoglobin to hemoglobin. Hemoglobin binds and delivers oxygen to the body's tissues, while methemoglobin does not.

Methemoglobin is produced when heme ferrous iron molecules (Fe2+) are oxidized to ferric iron (Fe3+), which are unable to bind oxygen. In addition, the remaining ferrous iron molecules have increased affinity for oxygen, and are less likely to release oxygen to the peripheral tissues (21).

Normally, the oxidation of hemoglobin occurs at a slow rate –– approximately 1% of red blood cells contain methemoglobin (3). An increase in methemoglobin (methemoglobinemia) is caused either by an increased production (for example, triggered by the ingestion of poison, street drugs, and certain medications) or be decreased removal (for example, kidney failure). Symptoms include a bluish skin color (cyanosis), headache,

fatigue, and shortness of breath. When levels of methemoglobin approach 10%, cyanosis occurs. Higher levels may cause seizures, and levels above 30% are life threatening.

Most cases of methemoglobinemia are acquired. The antibiotics dapsone and chloroquine, anesthetics such as benzocaine, and rasburicase, have all been associated with methemoglobinemia.

Much less commonly, methemoglobinemia is inherited. There are 2 main causes of hereditary methemglobinemia –– Hemoglobin M disease and CYB5R3 deficiency. The former is an autosomal dominant disorder in which a variant occurs in one of the globin chains and results in defective hemoglobin. The latter, CYB5R3 deficiency, is a rare autosomal recessive disorder that is more common in specific populations, for example, Athabascan Alaskans, and Navajo Indians. A variant in the *CYB5R3* gene results in 2 forms of CYB5R deficiency: in type 1, the mutated enzyme is unstable with reduced activity; type 2 is lethal in early pregnancy because the mutated enzyme has no activity (3, 22, 23).

In type 1 CYB5R3 deficiency, the mutated enzyme is expressed in all tissues – but the enzyme is only deficient in red blood cells. This is because unlike other cell types, mature red blood cells lack the ability to synthesize new proteins. Therefore the mutated enzyme, which is easily degraded, is not replaced (22).

Individuals who have 2 copies of the *CYB5R3* variant (homozygous) have high levels of methemoglobin (up to 40%) and may appear cyanotic. However, their symptoms are typically mild ("blue but well") and lifespan is normal – this is because they are adapted to accommodate cyanosis, for example, they have an increased red blood cell mass (24).

In contrast, individuals who have one copy of the *CYB5R3* variant (heterozygous) have lower levels of methemoglobin (approximately 10%) and do not have cyanosis. However, because these individuals are not adapted, they are at high risk of developing life-threatening methemogolobinemia if they are treated with medications that can increase methemoglobin levels (3).

The drug label for rasburicase warns that rasburicase can result in methemoglobinemia in some individuals, and warms to immediately and permanently discontinue rasburicase in individuals developing methemoglobinemia (1).

Linking Gene Variation with Treatment Response

G6PD

Although evidence that links the G6PD status of individuals taking rasburicase with an increased risk of hemolytic anemia is limited to case reports, it is well known that hydrogen peroxide, which is produced during rasburicase therapy, can cause acute hemolysis in individuals with G6PD deficiency. Therefore, many countries, including the US, have warned that the use of rasburicase is contraindicated in individuals with G6PD deficiency (2, 21, 25-33).

CYB5R3

There are no published reports of methemoglobinemia attributed to the combination of rasburicase therapy with an underlying CYB5R3 deficiency. According to the drug label, rasburicase-induced methemoglobinemia occurs in less than 1% of individuals, and their CYB5R3 status is not stated. The drug label states that "it is not known whether individuals with deficiency of cytochrome b5 reductase (formerly known as methemoglobin reductase) or of other enzymes with antioxidant activity are at increased risk for methemoglobinemia or hemolytic anemia" (1).

Genetic Testing

The NIH Genetic Testing Registry, GTR, displays genetic tests that are available for rasburicase response, and the genes *G6PD* and *CYB5R3*. Molecular genetic testing can be used to confirm the diagnosis of G6PD or CYB5R3 deficiency. Testing may also be used to screen females with a family history of G6PD deficiency to see if they are carriers.

G6PD 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 (9). 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 (2).

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* gene to their daughters, but not to their sons (12, 34).

The FDA recommends that individuals at risk of G6PD deficiency be screened for G6PD deficiency before starting rasburicase therapy. However, individuals of all ancestries may be G6PD deficient (worldwide prevalence of 5%). Therefore, caution must be taken in all individuals when initiating rasburicase 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. 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 levels should be performed 23 months after a blood transfusion or hemolytic episode. Note, false negatives have been reported (2, 12, 35).

In men, if genetic testing was used to determine that an individual was positive for G6PD deficiency, the use of rasburicase would be contraindicated. However, a negative result cannot be entirely relied upon because only a small subset of G6PD variants are routinely tested for via targeted assays (2, 4, 12, 34, 36). In addition, G6PD phenotype may be unpredictable in heterozygous females because of X-chromosome inactivation, which can happen in a variable percentage of somatic cells.

Universal neonatal screening programs for G6PD deficiency are employed in some countries with a high incidence of G6PD deficiency (more than 3–5% of males) (37). These populations are primarily in Asia, Africa, along the Mediterranean and in the Middle East. Screening either uses quantitative enzyme activity assays, or the fluorescent spot test that visually identifies NADPH, which is produced by G6PD (if the blood spot does not fluoresce, the test is positive for G6PD deficiency) (2).

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.

2019 Statement from the US Food and Drug Administration (FDA)

Hemolysis

Rasburicase is contraindicated in patients with G6PD deficiency because hydrogen peroxide is one of the major by-products of the conversion of uric acid to allantoin. In clinical studies, hemolysis occurs in <1% patients receiving rasburicase; severe hemolytic reactions occurred within 2–4 days of the start of rasburicase. Immediately and permanently discontinue rasburicase administration in any patient developing hemolysis. Institute appropriate patient monitoring and support measures (e.g., transfusion support). Screen patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting rasburicase.

Methemoglobinemia

In clinical studies, methemoglobinemia occurred in <1% patients receiving rasburicase. These included cases of serious hypoxemia requiring intervention with medical support measures. It is not known whether patients with deficiency of cytochrome b5 reductase (formerly known as methemoglobin reductase) or of other enzymes with antioxidant activity are at increased risk for methemoglobinemia or hemolytic anemia. Immediately and permanently discontinue rasburicase administration in any patient identified as having developed methemoglobinemia. Institute appropriate monitoring and support measures (e.g., transfusion support, methylene-blue administration).

Please review the complete therapeutic recommendations that are located here: (1).

2014 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

[…]

As stated above, rasburicase use is contraindicated by the FDA, the European Medicines Agency, and the Pharmaceuticals and Medical Devices Agency in those with G6PD deficiency. If, on the basis of genotyping, a deficient status can be unambiguously assigned to a patient, that would be a sufficient contraindication to the use of rasburicase. However, due to the limitations of genetic testing (discussed above), in most cases it is necessary to perform G6PD enzyme testing to assign G6PD status.

The FDA recommends that patients at higher risk of G6PD deficiency, such as those with African or Mediterranean ancestry, be tested for G6PD deficiency before initiation of rasburicase. However, it should be noted that patients of all ancestries may be G6PD deficient. The drug labels do not specifically mention genetic testing, but with the increased availability of genetic test results some patients may be diagnosed with G6PD deficiency preemptively; if so, such definitive results could be used to preclude prescribing of rasburicase and potentially other oxidative drugs even in the absence of G6PD enzyme activity results.

Pediatrics. Much of the evidence relating G6PD deficiency to rasburicase-induced hemolysis and methemoglobinemia was generated in neonates or children (Supplementary Table S7 online), and thus these guidelines apply to neonates, children, and adults.

[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.*

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
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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