

Supplement to:

Expanded Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Medication Use in the Context of *G6PD* Genotype

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GUIDELINE UPDATES

The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for medication use in the context of *G6PD* genotype is published in full on the CPIC website (1). Relevant information will be reviewed periodically and updated guidelines published online.

LITERATURE REVIEW

Drugs were selected for inclusion in the literature review if they were considered potentially unsafe in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to an increased risk of drug-induced hemolysis by the U.S. Food and Drug Administration (FDA) or another regulatory agency (as curated in PharmGKB, www.pharmgkb.org; see **Table S3**), the Italian G6PD Deficiency Association (www.g6pd.org), the 1989 World Health Organization (WHO) Working Group on G6PD deficiency (2), and/or one of five published reviews (3-7), and the drug is used in clinical practice today.

The PubMed® database (1966 to September 2021) was searched for the following keywords: (drug keywords) AND (G6PD OR glucose-6-phosphate dehydrogenase OR G-6-PD). The drug-specific keywords are listed below:

- **4-aminosalicylic acid:** aminosalicylic acid OR 4-aminosalicylic acid OR p-aminosalicylic acid OR para-aminosalicylic acid OR 4-amino-2-hydroxybenzoic acid OR Paser
- **aspirin:** aspirin OR acetylsalicylic acid
- **chloramphenicol:** chloramphenicol OR Chloromycetin
- **chloroquine:** chloroquine OR Aralen
- **chlorpropamide:** chlorpropamide

- **ciprofloxacin:** ciprofloxacin OR Cipro
- **dabrafenib:** dabrafenib OR Tafinlar
- **dapsone:** dapsone OR diaminodiphenyl sulfone OR Aczone
- **dimercaprol:** dimercaprol OR British anti-Lewisite OR BAL in Oil
- **doxorubicin:** doxorubicin OR Lipodox OR Doxil OR Adriamycin OR Rubex OR Caelyx
OR Myocet
- **furazolidone:** furazolidone OR furoxone OR Dependal-M
- **gliclazide:** gliclazide
- **glimepiride:** glimepiride
- **glipizide:** glipizide
- **glyburide:** glyburide OR glibenclamide
- **hydroxychloroquine:** hydroxychloroquine OR Plaquenil
- **mafenide:** mafenide OR Sulfamylon
- **mepacrine:** mepacrine OR quinacrine OR Atabrine
- **mesalazine:** mesalazine OR 5-aminosalicylic acid OR 5-ASA OR mesalamine OR
Canasa OR Delzicol OR Asacol HD OR Pentasa OR Apriso OR Lialda OR **sfRowasa**
- **methylene blue:** methylene blue OR methylthioninium chloride
- **moxifloxacin:** moxifloxacin OR Avelox OR Avalox OR Vigamox OR Moxeza
- **nalidixic acid:** nalidixic acid OR NegGram OR Nevigramon OR Wintomylon
- **nicorandil:** nicorandil
- **nitrofurantoin:** nitrofurantoin OR Macrobid OR Macrochantin OR Furadantin
- **nitrofurazone:** nitrofurazone OR Furacin
- **nitrofurantoin:** nitrofurantoin OR Macrobid OR Macrochantin OR Furadantin
- **norfloxacin:** norfloxacin OR Noroxin

- **ofloxacin:** ofloxacin OR Floxin OR Ocuflor
- **pegloticase:** pegloticase OR Krystexxa
- **phenazopyridine:** phenazopyridine OR Pyridium
- **probenecid:** probenecid OR Probalan
- **quinine:** quinine OR Quaaloon
- **rasburicase:** rasburicase OR urate oxidase OR uricase OR Elitek OR Fasturtec
- **sodium nitrite:** sodium nitrite
- **sulfacetamide:** sulfacetamide OR Klaron
- **sulfadiazine:** sulfadiazine
- **sulfadimidine:** sulfadimidine OR sulfamethazine OR sulfadimerazine OR sulfadimezine
OR sulphadimethylpyrimidine
- **sulfamethoxazole:** sulfamethoxazole OR co-trimoxazole OR Bactrim OR Septra
- **sulfanilamide:** sulfanilamide OR sulphanilamide
- **sulfasalazine:** sulfasalazine OR salicylazosulfapyridine OR Azulfidine
- **sulfisoxazole:** sulfisoxazole OR sulfafurazole
- **tafenoquine:** tafenoquine OR Krintafel OR Arakoda
- **tolazamide:** tolazamide
- **tolbutamide:** tolbutamide
- **toluidine blue:** toluidine blue OR tolonium chloride
- **trametinib:** trametinib OR Mekinist
- **vitamin C:** ascorbic acid OR vitamin C OR moviprep
- **vitamin K:** menadione OR menaphthone OR phytomenadione OR vitamin K1 OR
vitamin K3 OR vitamin K

Study inclusion criteria included publications that incorporated analyses for the association between G6PD deficiency (diagnosed by enzyme activity and/or genotype) and medication-induced acute hemolytic anemia (AHA). The search was limited to studies written in the English language. Following the application of these criteria, 248 publications were identified. Of these, the full text was accessible for 241 publications. These publications were reviewed and included in the evidence table (**Table S1**). Additional studies documenting the widespread use of a particular drug (e.g., aspirin, sulfamethoxazole) with no reported AHA in the study population was also considered as supporting evidence for the lack of association between the drug and AHA in G6PD deficient patients.

For rasburicase, the literature search focused on articles published from January 2013-September 2021, as the prior CPIC guideline for *G6PD*/rasburicase encompassed literature that was published before this time (8).

For vitamin C and vitamin K, a systematic review (9) was used to summarize the available literature up until November 2015, and a separate literature review was conducted from November 2015-September 2021 to capture new articles.

Primaquine is a special case in that the association between G6PD deficiency and primaquine-induced AHA is well-established and has been known for over 50 years (10, 11). Therefore, the literature review for primaquine focused on articles describing the safety and efficacy of lower doses in patients with G6PD deficiency, which provided a basis for the therapeutic recommendations provided in the guideline (**Table 6, main manuscript**). The keywords used for the primaquine literature searches included 1) primaquine AND ("low-dose" OR "low dose"); and 2) primaquine AND ("8 weeks" OR "eight weeks"). The timeframe was

1966 to September 2021. The first search yielded an additional 10 articles for inclusion, and the second search yielded an additional six articles for inclusion (**Table S1**).

There are a few limitations to note regarding this literature review. First, given the fact that G6PD deficiency has been known for decades, relevant literature may have been published prior to the year that the PubMed® database index begins (1966). The reference lists of G6PD-related review articles were checked for articles that the literature search may not have captured. Second, although every effort was made to access the full text of all potentially relevant articles returned in the literature searches, the full text of some older publications (n =7), especially those from international journals, were not accessible to the authors and thus could not be assessed in the context of the larger evidence body. These articles were screened based on title and/or abstract as being potentially relevant, but without full-text access, it was impossible to determine whether that was actually the case.

GENETIC TEST INTERPRETATION

Although in most populations a few alleles account for the vast majority in deficient patients, sequencing may be required to detect other rare alleles. The detection of one Class I-III allele in those with one X chromosome or two Class I-III alleles in those with two X chromosomes is informative for predicting G6PD deficiency, whereas a ‘negative’ genotype result would not definitively rule out G6PD deficiency, particularly in those with two X chromosomes. Although an enzyme activity test would be needed to assess G6PD status in patients with non-definitive genetic tests, the limitations of the G6PD activity tests may also result in misclassifications (12).

AVAILABLE GENETIC TEST OPTIONS

Commercially available genetic testing options change over time. The Genetic Testing Registry provides a central location for voluntary submission of genetic test information by providers and is available at <http://www.ncbi.nlm.nih.gov/gtr>. Newborn screening for G6PD deficiency is rare (13, 14). Desirable characteristics of pharmacogenetic tests, including naming of alleles and test report contents, have been extensively reviewed by an international group, including CPIC members (15). CPIC recommends that clinical laboratories adhere to these test reporting standards. CPIC gene-specific tables adhere to these allele nomenclature standards. Moreover, these tables (***G6PD* Allele Definition Table**, ***G6PD* Allele Functionality Table**, and ***G6PD* Allele Frequency Table**) may be used to assemble lists of known functional and actionable genetic variants and their population frequencies, which may inform decisions as to whether pharmacogenetic tests are adequately comprehensive with the interrogated alleles (1, 16).

LEVELS OF EVIDENCE

For this CPIC guideline, the evidence was reviewed primarily to determine the strength of evidence linking a drug with AHA that was related to G6PD deficiency. The vast majority of published reports for these drugs were uncontrolled case reports, and there were often no high quality controlled studies. The data summarized in **Table S1** are graded on a scale of high, moderate, and weak, based upon the level of evidence.

The criteria applied for assigning evidence level for association of the drug with G6PD deficiency-associated hemolysis included:

High:

- Good quality studies supporting G6PD involvement with control groups; OR

- Case reports with strong biological mechanism (e.g, production of hydrogen peroxide), especially if the drug is rarely used; AND
- No convincing contradictory data.

Moderate:

- Medium quality studies supporting G6PD involvement with control group; OR
- Case reports with plausible mechanism; AND
- Little to no convincing contradictory data.

Weak:

- Case reports or *in vitro* evidence only, especially for commonly used drugs; OR
- Studies that refute G6PD involvement with no convincing supportive studies;
AND
- No convincing mechanistic data.

The criteria applied for assigning evidence level for a lack of association of the drug with G6PD deficiency-associated hemolysis included:

High:

- Good quality studies supporting lack of G6PD involvement with control groups;
AND
- No convincing contradictory data.

Moderate:

- Medium quality studies supporting lack of G6PD involvement with control group;
AND
- Little to no convincing contradictory data

Weak:

- Weak/flawed studies supporting lack of G6PD involvement; OR
- Case reports or *in vitro* evidence only, especially for commonly used drugs

STRENGTH OF RECOMMENDATIONS

CPIC's therapeutic recommendations are based on weighing the evidence from a combination of preclinical functional and clinical data. Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. CPIC uses a slight modification of a transparent and simple system for recommendations adopted from the rating scale for evidence-based guidelines on the use of antiretroviral agents (17):

- **Strong** recommendation for the statement: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.
- **Moderate** recommendation for the statement: There is a close or uncertain balance as to whether the evidence is high quality and the desirable effects clearly outweigh the undesirable effects.
- **Optional** recommendation for the statement: The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.
- **No recommendation:** There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.

ASSIGNING RISK LEVEL

As discussed in the main manuscript, due to the large number of drugs putatively linked to AHA in the setting of G6PD deficiency, an additional step was added to this CPIC guideline to assign drugs into one of three groups: 1) those that can be considered high risk for AHA in the presence of G6PD deficiency; 2) those that are considered medium risk in G6PD deficiency; 3) and those that can be considered low-to-no risk (**Table 2, Main Manuscript**). In order to assign drugs into the high, medium, and low-to-no risk groups, the authors considered not only the strength of the evidence in the primary peer-reviewed literature, but also the frequency of drug use; the presence, strength, and consistency of regulatory agency warnings; and the presence or absence of a biological mechanism by which reactive oxygen species might be generated and contribute to red cell hemolysis in the setting of G6PD deficiency. Authors were mindful that regulatory warnings may have hindered the use of some medications in G6PD deficiency, thus resulting in a lack of available studies of the drug in G6PD deficiency. In addition, the paucity of reports of hemolytic anemia for widely used drugs, such as sulfonamides, sulfonyleureas, or low-dose aspirin, coupled with the lack of any positive studies, strongly suggests that such drugs are not associated with AHA in G6PD deficiency.

Drugs were classified as into high risk, medium risk, and low-to-no risk categories, based on their risk of inducing AHA in patients with G6PD deficiency, as determined by the criteria below:

High Risk:

- High-level evidence + rarely used drug; OR
- Moderate-level evidence + rarely used drug with regulatory warnings for patients with G6PD deficiency; OR

- Moderate-level evidence + strong biological mechanism for risk in patients with G6PD deficiency

Medium Risk:

- Moderate-level evidence without a strong biological mechanism for risk in patients with G6PD deficiency; OR
- Weak evidence + rarely used drug; OR
- Weak evidence + strong regulatory warnings for patients with G6PD deficiency that may have hindered use in these patients; OR
- Weak evidence + strong biological mechanism for risk in patients with G6PD deficiency

Low-to-no Risk:

- Weak evidence + commonly used drug; OR
- Weak evidence + mild or inconsistent regulatory warnings for patients with G6PD deficiency

HIGH RISK DRUGS

See the **Main Manuscript** for a discussion of the high risk drugs rasburicase, pegloticase, and primaquine (standard dose) and below for a summary of the other high risk drugs. High risk drugs are those that should be avoided in patients with G6PD deficiency.

Dapsone

Dapsone is a commonly used sulfone anti-leprosy drug, interfering with folate synthesis. It is used for treatment and sometimes prophylaxis, acutely and chronically, for a wide range of

diseases, including acne, *Pneumocystis jirovecii*, dermatitis herpetiformis, and toxoplasmosis, and is on the WHO list of essential medicines (18). It is available as an oral tablet and topical gel. Adult doses range widely depending on indication, from 50 mg/week to 300 mg/day.

Dapsone may act as an oxidizing agent, which may contribute to its ability to induce AHA in G6PD deficiency. In addition, it has numerous immunologic effects (e.g., immunosuppression), which most likely account for its suppression of dermatitis herpetiformis

Dapsone is considered in the high-risk category because evidence linking it to AHA is moderate to high, and because it has been the subject of multiple regulatory warnings for years. There are multiple case reports of AHA after dapsone, although few studies with controls. There is some evidence that dapsone may cause AHA in patients regardless of G6PD status (19-26), and there are a few clinical studies suggesting that topical dapsone (27, 28) and lower-dose prophylactic dapsone may not cause AHA in G6PD deficient patients (29-31). These negative studies are balanced by the large number of case reports, regulatory warnings, and preclinical studies showing AHA after dapsone exposure (32-34).

Dapsone should generally be avoided in patients with G6PD deficiency; due to some conflicting studies, this recommendation is moderate and not strong. As for all drugs, the warning is dependent on dosage; higher dosages are more likely to result in AHA than lower dosages.

Methylene Blue

Methylene blue is used to treat methemoglobinemia, especially drug-induced, and is on the WHO list of essential medicines (Antidotes and Other Substances used in Poisonings) (35). It has also been trialed in combination with other agents, including chloroquine for the treatment of

falciparum malaria. It is in the high-risk category with moderate strength of recommendation with the evidence linking it to AHA being moderate due to many case studies where it has been used to treat methemoglobinemia caused by specific chemical poisonings (36-38), drug-induced (39-41) or idiopathic (42-44). There are also case reports where it has not contributed to AHA but these have been mainly where it has been used for rasburicase-induced methemoglobinemia (45-47) and in clinical trials for falciparum malaria (48, 49).

The large number of case reports and regulatory warnings indicate that methylene blue should be avoided in patients with G6PD deficiency.

Tafenoquine

Tafenoquine is a newer antimalarial and is indicated for prophylaxis against all malarial species and as anti-relapse treatment for *Plasmodium vivax* and *Plasmodium ovale*. Tafenoquine is considered in the high-risk category because the level of evidence is high, there are regulatory agency warnings against its use, and being an oxidative 8-aminoquinoline, has the same AHA mechanisms as primaquine. There are sparse data suggesting that in females (n=2), heterozygotes with G6PD activity intermediate between deficient and normal activities, may have AHA after tafenoquine, even at lower doses (50). Two studies of tafenoquine safety included patients with normal G6PD activity, defined as those with G6PD enzyme levels at least 70% of normal (51, 52). Thus, some have suggested that tafenoquine be limited to those with G6PD enzyme levels that are at least 70% of normal (53), whereas Class IV (normal) alleles are those with at least 60% normal activity. It is possible that an individual classified as normal by a clinical laboratory would have activity between 60% and 70% of normal, and it is recommended that tafenoquine be

withheld in such patients (53). A recent paper details the use of a commercial assay and percentage-based reporting for G6PD activity (54).

Toluidine Blue

This dye has been used in histopathology to stain specific tissues and cells and was used *in vivo* to aid in the surgical removal of specific tumors and biopsy identification. It is in the high-risk category with moderate strength of recommendation as the evidence linking it to AHA is weak based on a single case report (55), but it is structurally similar to methylene blue, which is high risk. Given its now rare use, regulatory agencies and the WHO (2018) no longer issue a warning statement.

MEDIUM RISK DRUGS

See the **Main Manuscript** for a discussion of the medium risk drugs primaquine (0.75 mg/kg or 45 mg once weekly for 8 weeks) and nitrofurantoin. Medium risk drugs are those that should be used at standard doses with caution and with close monitoring for anemia.

LOW-TO-NO RISK DRUGS

See the **Main Manuscript** for a discussion of the low-to-no risk drugs sulfamethoxazole and primaquine (single low dose, 0.25 mg/kg, for *Plasmodium falciparum* malaria) and below for a summary of the other low-to-no risk drugs. There is no reason to avoid a low-to-no risk drug based on G6PD status at standard doses.

4-Aminosalicylic Acid

4-aminosalicylic acid (also known as p-aminosalicylic acid) is an antibiotic that is used to treat multi-drug resistant tuberculosis in combination with other antitubercular drugs. It is available as a 4-gram packet of extended-release granules and 500 mg tablets for oral use. In adults, its dosing is 4 grams given two to three times daily as part of an antitubercular combination regimen, and the agent is listed on the WHO list of essential medicines (56).

4-Aminosalicylic acid is considered in the low-to-no risk category with optional strength of recommendation because there are no regulatory warnings, and the evidence linking it to AHA is weak, based on one study of moderate *in vitro* evidence of safety (57) and one weak case report (58). 4-aminosalicylic acid can be used without regard to G6PD status.

Aspirin \leq 1 g/day

Aspirin is a widely used medication on the WHO list of essential medicines (56). Indications for aspirin include analgesia and prevention of arterial thrombosis (as an antiplatelet agent), Kawasaki disease, and rheumatic fever. Adult dosing ranges from 81 mg daily to 8 g daily in divided doses; pediatric dosing ranges from 10 mg/kg/dose every four to six hours to 100 mg/kg/day.

Aspirin at less than one gram is considered in the low-to-no risk with moderate strength of recommendations because the evidence linking AHA is weak, several studies show its safety in G6PD deficiency, and a large cohort of patients administered aspirin less than one gram did not experience AHA (**Table S1**). Aspirin less than one gram can be used without regard to G6PD status. Aspirin greater than one gram daily is considered to have no recommendation to guide clinical practice at this time because the evidence for the association is mixed, with neither direction dominating.

Chloramphenicol

Chloramphenicol acid is an orally and parenterally administered antibiotic, available since the early 1950s, used to treat serious infections, with adult dosages ranging from about 50 to 100 mg/kg/day. Because of adverse effects, its use is now generally reserved for infections that cannot be treated with safer antibiotics. It has been very widely used in the past and remains on the WHO list of essential medicines (56).

Chloramphenicol is considered in the low-to-no risk category with a moderate strength of recommendation because the evidence linking it to AHA is weak (case reports, weak *in vitro* evidence), and several studies show safety in G6PD deficiency (59-67). Because it is generally used for serious infections, all reports of AHA are complicated by the presence of concurrent infection. Chloramphenicol may be used without regard to G6PD status.

Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine are anti-protozoal agents used to treat or prevent malaria and some other infections, and they have also been used (particularly hydroxychloroquine) in some immune-mediated diseases, such as rheumatoid arthritis, systemic lupus erythematosus and sarcoidosis. There is wide variability in daily dosages for both adults and children. Both drugs are, or have been, widely used (18, 68).

Chloroquine and hydroxychloroquine are considered in the low-to-no risk category with a moderate strength of recommendation because the evidence linking both drugs to AHA is weak, and several studies and case reports show safety of these drugs in G6PD deficiency (48, 49, 69-75).

Dimercaprol

Dimercaprol is an antidote for arsenic, gold, mercury, and lead poisoning. It is available as a parenteral product for deep intramuscular injection, with initial adult doses ranging from 2.5-5 mg/kg with subsequent frequency and/or dosing adjustments for 10 days of therapy. This agent is listed on the WHO list of essential medicines (56).

Dimercaprol is considered in the low-to-no risk category with optional strength of recommendation because the evidence linking it to AHA is weak, based on one weak case report (76). Dimercaprol can be used without regard to G6PD status.

Doxorubicin

Doxorubicin is one of the most widely used antineoplastics, used for a number of different solid and hematologic malignancies worldwide. Doxorubicin is on the WHO list of essential medicines (56).

Doxorubicin is considered in the low-to-no risk category with optional strength of recommendation because the evidence linking it to AHA is weak, based on a case report, with at least one case of it being safely given to a G6PD deficient patient with no AHA (77).

Doxorubicin can be used without regard to G6PD status.

Furazolidone

Furazolidone is an antiprotozoal agent that is most commonly used for the treatment of cholera-associated diarrhea and diarrhea produced by other susceptible organisms such as *Giardia lamblia*.

Furazolidone is considered in the low-to-no risk category with optional strength of recommendation because the evidence linking it to AHA is weak, based on one case report (78) and one retrospective cohort showing safety in 23 patients with G6PD deficiency (61). Furazolidone can be used without regard to G6PD status.

Glyburide (Glibenclamide)

Glyburide is a sulfonylurea antidiabetic agent that stimulates insulin release from pancreatic beta cells, reduces hepatic glucose output, and increases insulin sensitivity in peripheral sites. It is available in a variety of oral tablet strengths and different formulations. Adult dosing with the conventional oral tablets may range from 1.25-5 mg daily, or, with the micronized tablets may range from 0.75-3 mg daily upon therapy initiation followed by dosage adjustments guided by glycemic response.

Glyburide is considered in the low-to-no risk category with optional strength of recommendation because the evidence linking it to AHA is weak, based on three case reports (79-81). Based upon review of the available evidence and extensive use, there is no reason to consider G6PD status when using glyburide.

Mafenide

Mafenide is a topical antibiotic mostly used for the treatment and prevention of wound infections in patients with severe burns.

Mafenide is considered in the low-to-no risk category with optional strength of recommendation because the evidence linking it to AHA is weak, based on one case report (82). Mafenide can be used without regard to G6PD status.

Phenazopyridine

Phenazopyridine is a local anesthetic prescribed for dysuria, with adult dosing ranging from 190 mg to 200 mg three times a day for a maximum of two days. Phenazopyridine is readily available over the counter to patients without a prescription in many countries

Phenazopyridine at standard dosing is considered in the low-to-no risk category with optional strength of recommendation because the evidence linking it to AHA is weak, based on few case reports in which patients also had concomitant risk factors (i.e., infection, concomitant medications) or supratherapeutic dosing (83-86), and given its widespread use. Phenazopyridine can be used without regard to G6PD status.

Quinine

Quinine is an antimalarial agent often used in combination with other agents, and it disrupts parasite transcription and replication processes. Globally, it is available for parenteral and oral use. Depending upon the oral product's salt base and country of manufacture, the dosage of quinine may differ. The US-manufactured capsule dosage, based on Centers for Disease Control and Prevention guidance and geographic region of acquired infection, is 648 mg every 8 hours for 3 to 7 days used in combination with other antimalarial agents. For other countries of manufacture, such as Canada, the recommended dose is 600 mg every 8 hours for 3 to 7 days used in combination with other antimalarial agents. This agent is listed on the WHO list of essential medicines (56).

Quinine is considered in the low-to-no risk category with optional strength of recommendation because the evidence linking it to AHA is weak based on limited case reports

(87-90), while two prospective cohorts and *in vitro* evidence did not attribute quinine to AHA in G6PD deficiency (91-93). Based upon review of the available evidence and the drug's widespread global use, it appears unnecessary to consider G6PD status when using quinine.

Quinolones

Ciprofloxacin, norfloxacin, ofloxacin, and moxifloxacin are fluoroquinolones, whereas nalidixic acid, which is no longer used in many countries, does not contain a fluorine atom. Ciprofloxacin is on the WHO list of essential medicines (56). Quinolones are broad-spectrum antibiotics that are increasingly reserved for treating infections when other antibiotics are ineffective or contraindicated.

Quinolone antibiotics are considered to be in the low-to-no risk category for G6PD deficiency with optional strength of recommendation because the evidence linking them to AHA is weak (ciprofloxacin: (94), (95), (96); norfloxacin: (97); nalidixic acid: (98), (99)) and for ofloxacin, ophthalmic use was safe in a G6PD deficiency case (100); there are no case reports or studies with moxifloxacin. The quinolones can be used without regard to G6PD status.

Sulfasalazine

Sulfasalazine is an anti-inflammatory medication most commonly used to treat autoimmune conditions such as ulcerative colitis and rheumatoid arthritis. This agent is listed on the WHO list of essential medicines (56).

Sulfasalazine is considered in the low-to-no risk category with optional strength of recommendation because the evidence linking it to AHA is weak, based on one case report (101). Sulfasalazine can be used without regard to G6PD status.

Sulfonamide Antibiotics

Sulfamethoxazole, sulfadiazine, sulfadimidine, sulfanilamide, and sulfisoxazole are sulfonamide antibiotics. Silver sulfadiazine is used topically for the treatment and prevention of wound infections in patients with severe burns. Sulfadiazine and silver sulfadiazine are on the list of WHO essential medicines (56).

The sulfonamide antibiotics are considered in the low-to-no risk category with optional strength of recommendation because the evidence linking them to AHA is weak (sulfadiazine: (78), (102); topical sulfadiazine: (103); sulfadimidine: (104); sulfanilamide: (66), (105); sulfisoxazole: (106), (107), (108)). Additionally, sulfisoxazole administration was found to be safe in healthy volunteers with G6PD deficiency (109). Sulfamethoxazole is discussed in more detail in the **Main Manuscript**. The sulfonamide antibiotics can be used without regard to G6PD status.

Tolbutamide

Tolbutamide is a sulfonylurea antidiabetic agent that stimulates insulin release from pancreatic beta cells, reduces hepatic glucose output, and increases insulin sensitivity in peripheral sites. It is available as an oral tablet. Adult initial doses range from 1-2 grams daily in single or divided doses, and adult maintenance doses range from 0.25-3 grams daily, although seldom exceed more than 2 grams daily.

Tolbutamide is considered in the low-to-no risk category with optional strength of recommendation because the evidence linking it to AHA is weak, based on two case reports

(110, 111). Based upon review of the available evidence, there is no reason to consider G6PD status when using tolbutamide.

Vitamins C and K

Vitamin C is a water-soluble vitamin used for wound healing, burns, scurvy, methemoglobinemia, and nutritional support. Adult dosages vary based on indications, with a dosing range of 100 mg/day to 10 g every six hours; pediatric dosing ranges from 50 mg weekly to 200 mg daily. Vitamin C is readily available over the counter and is an additive to many immune-boosting supplements. Vitamin K is a fat-soluble vitamin commonly prescribed as nutritional support and as a reversal agent for vitamin K antagonists. Both vitamin K and vitamin C are on the WHO list of essential medicines (56).

Vitamin K and vitamin C at standard dosing are considered in the low-to-no risk category with a moderate strength of recommendation because the evidence linking them to AHA is weak (case reports, weak *in vitro* evidence), and several studies show their safety in G6PD deficiency (9). Although there are case reports of AHA in patients with G6PD deficiency who received very high doses of intravenous vitamin C (112, 113), vitamin C and vitamin K can be used at standard doses without regard to G6PD status.

DRUGS WITH NO THERAPEUTIC RECOMMENDATIONS

For a subset of the drugs evaluated as part of the literature search (n = 15), no relevant articles were identified that linked the drug to an increased risk of AHA in the setting of G6PD deficiency, although they were considered by one or more sources to be a potential risk for patients with G6PD deficiency. Thus, no therapeutic recommendations regarding the use of these drugs in G6PD deficiency has been made (CPIC Level C). In addition, for doses of aspirin >1

g/day, there was insufficient data to assess at what dose aspirin may cause AHA in patients with G6PD deficiency and whether any hemolysis noted in case reports was the result of infection rather than the drug itself.

The decision to classify these drugs as having no recommendation was somewhat controversial, because many of the “low-to-no” risk drugs had so little evidence (e.g., a single case report) that the evidence could be considered comparable to “no evidence.” The authors considered the options of making all drugs with little to no evidence as “no recommendation” versus making all drugs with little to no evidence as “low-to-no” risk. In the end, it was decided to classify drugs with **little** evidence as “low-to-no” risk and to classify drugs with **no** evidence as “no recommendation,” although many of the drugs with no evidence are, or have been, extremely widely used worldwide (e.g., certain sulfonylureas, probenecid) with few or no reports of AHA (even without G6PD status known), and thus are likely to be “low-to-no” risk drugs.

G6PD GENETIC VARIANT NOMENCLATURE AND WORLD HEALTH

ORGANIZATION CLASS

Criteria for the identification and characterization of *G6PD* alleles were established by the WHO Scientific Group starting in 1967 (114), based primarily on samples from hemizygous persons. Characteristics used to classify alleles have included G6PD activity in red blood cells, electrophoretic migration as compared to the normal B enzyme, thermal stability, and Michaelis constant for G6PD and rate of utilization. Nomenclature guidelines were outlined before the cDNA position for each allele was reported and suggested the use of geographical or trivial names for new alleles.

Along with being grouped by the amount of evidence that existed for a particular allele, in 1971 the *G6PD* alleles were divided into five classes (class I-V), as determined by the extent

of enzyme deficiency and associated clinical manifestations (**Table S2**) (115). Standardized criteria for determining the class were defined and included erythrocyte activity level and electrophoretic mobility performed on samples from hemizygous persons. It should be noted that the alleles were “somewhat arbitrarily divided into five classes” and that the “distinction between these classes is not always clear” (115). For example, although the Mediterranean variant (rs5030868 563C>T) is assigned a class II definition, it has also been associated with chronic nonspherocytic hemolytic anemia (CNSHA), consistent with the definition of class I alleles (115). Some class I alleles have higher enzyme activity *in vitro* than those of class III alleles (115) and *in vivo* enzyme activity can be altered by numerous factors (3, 4). This class system was again reported in a WHO update article with slight differences in enzyme activity for class IV (normal activity described as 60-150%) and class V (described simply as increased activity) (2). This five-class system is currently being updated by WHO: in 2022, the WHO assembled a working group to revise this classification system (13); however, alleles have not yet been reclassified according to the proposed new system, so this CPIC guideline continues to use the legacy classifications I-IV. Since being issued (116), most have recommended that the clinical phenotype is blurred between class II and III alleles and that these alleles should not be considered separate risk phenotypes, and thus this CPIC guideline treats Class II and III alleles identically as related to phenotype interpretation (i.e. both are associated with G6PD deficiency). In addition, because only one case of an increased activity (class V) has been reported, and the clinical significance and genetic variant are not clear, the WHO recommends removing class V (117). It has been suggested that four phenotype classes should be used (7, 114), as we have used in this guideline (**Table 1, main manuscript**). See the ***G6PD* Allele Definition Table, *G6PD***

Allele Functionality Table, and **G6PD Allele Frequency Table** for additional information about known *G6PD* alleles (1, 16).

Despite establishing nomenclature rules, the same genetic variant may have several different names; for example Mediterranean, Dallas, Panama, Sassari, Birmingham and Cagliari are all conferred by allele T at position 563 (rs5030868), but the enzyme variation was discovered in different populations (118). In addition, restriction endonuclease analysis of DNA revealed that several *G6PD* alleles thought to be the same had different underlying genetic variants; for example, the A- enzyme is a combination of the A variant (376A>G, rs1050829) and another variant, either 202A (rs1050828), or 680T (rs137852328), or 968C (rs76723693) (119). Worldwide estimates of G6PD deficiency prevalence and frequencies of alleles in major biogeographical ancestry groups can be found in the **G6PD Allele Frequency Table** online (1, 16). World distribution of *G6PD* deficient alleles correlates with malaria endemic regions, and this originally prompted the notion that G6PD deficiency confers protection from malaria. Populations from Asia, Africa and the Middle East are associated with the highest prevalence of G6PD deficiency (120).

G6PD HETEROZYGOTES

Determining G6PD phenotype in heterozygous persons (one normal class IV allele and one deficient class I-III allele) is not possible based on genetic testing alone due to X-linked chromosome inactivation. For example, in a study of Afghan refugees, the majority of people heterozygous for the Mediterranean allele (class II) had normal G6PD enzyme activity (by colorimetric assay), but one quarter were G6PD deficient (121). Variation in the percentage of G6PD deficient cells can change in the same individual over the space of a year, from 0% to

31% (122). Age is also a factor due to skewing of X chromosome inactivation. Newborn heterozygotes have a red cell population distribution skewed towards G6PD normal red blood cells, whereas heterozygous adults tend to show a more symmetrical distribution (123). Inactivation of the G6PD normal X chromosome increases in elderly heterozygotes, correlating with decreased G6PD activity levels (123, 124). This may mean as heterozygotes age they become more susceptible to clinical manifestations (124). For example, in a case report in which a novel class I allele was identified (Tondela), the mother was heterozygous and displayed chronic hemolytic anemia due to almost exclusive mRNA expression of the variant allele in reticulocytes resulting in G6PD deficiency; however two of her daughters were also heterozygous but asymptomatic with normal G6PD activity in red blood cells (125).

Determining whether a heterozygote is at increased risk of drug-induced hemolytic anemia is therefore not possible without measuring G6PD activity. Previous studies of dapsone treatment in A- heterozygote children with uncomplicated malaria infection seemed to show they were not at an increased risk of drug-induced AHA, until data from several studies was combined (126). The report showed that average risk is somewhere in between that of children with G6PD deficiency (hemizygous or homozygous A-) and those with normal G6PD, but individually this risk is highly variable due to X-linked mosaicism; with some individuals showing severe hemolysis upon dapsone treatment with a similar profile to that of deficient children, whilst others had very similar responses in hemoglobin levels as 'normal' children (126). The studies support the idea that the A- allele cannot be considered 'mild', as depending on the strength of the drug challenge, can cause severe life-threatening AHA. It is not known if these children may have had other genetic variants that could have contributed to the severity, and malaria infection should also be taken into account. For example, in a separate study, a 21-

month old girl heterozygous for A- suffered severe anemia with an anti-malarial regime containing methylene blue. She also however had high parasitemia, and overall heterozygotes were not reported to have a higher risk of hemoglobin decrease than wild-type children (127). As indicated above, it is possible that G6PD heterozygotes may have AHA from tafenoquine, with some claiming that a higher threshold (70% vs 60%) should be used to identify those with normal G6PD for purposes of identifying patients who can receive tafenoquine (50) There are little data to indicate whether AHA after other drugs is different in heterozygote versus other G6PD groups.

Compound heterozygotes (carrying two deficient class I-III alleles with different alleles) seem to be underreported in older literature; this may be due to most studies screening for a limited number of alleles rather than gene sequencing. Examples include: an 86 year-old Chinese female who displayed G6PD deficiency with the Canton/Viangchan genotype (class II/II) (124), Mediterranean/ Clatham (class II/II) and Asahi/ Clatham (class III/II) in Saudi women with G6PD deficiency (128). The assignment of compound heterozygous status is based on the assumption that each *G6PD* allele carries a deficient variant, rather than the two different variants residing on the same chromosome.

OTHER CONSIDERATIONS

Physiological factors other than genetic variants in the *G6PD* gene may result in differences in G6PD enzyme expression (129). As G6PD activity is usually measured in blood, G6PD activity test results are affected by various hematologic parameters. These include 1) critically low hemoglobin; 2) recent red blood cell transfusion; 3) elevated reticulocyte count; and 4) elevated white blood cell count (12).

Exogenous agents may cause hemolysis in an individual at one time when previously it had no effect (2). Susceptibility to drug-induced hemolytic anemia can be influenced by factors that are not constant; dosage and drug pharmacokinetics, the pharmacodynamic effects of the drug on G6PD activity, the presence of additional oxidative stresses such as concomitant drug administration, drug-drug interactions and infection, or baseline characteristics such as hemoglobin concentration and erythrocyte population age (4). Other inherited enzyme deficiencies may increase a patient's risk for hemolytic anemia, such as catalase deficiency (acatalasaemia) or the risk of methemoglobinemia, for example cytochrome b5 reductase deficiency or Hemoglobin M (130-132). It is also important to note that some drugs confer increased risk of hemolysis in everyone, regardless of G6PD status.

RESOURCES TO INCORPORATE PHARMACOGENETICS INTO AN ELECTRONIC HEALTH RECORD WITH CLINICAL DECISION SUPPORT

Clinical decision support (CDS) tools integrated within electronic health records (EHRs) can help guide clinical pharmacogenetics at the point of care (133-135). See <https://cpicpgx.org/cpic-guideline-for-g6pd/> for resources to support the adoption of CPIC guidelines within an EHR (1, 134). Based on the capabilities of various EHRs and local preferences, we recognize that approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common starting point for incorporating *G6PD* genotype results in an EHR to guide medication therapy.

Effective incorporation of pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. Pharmacogenetic test results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR. *G6PD* has

the added consideration that both phenotypic measures (of blood G6PD activity) and genotype may be available, and ideally EHR systems would incorporate both measures in clinical interpretations (12). To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted phenotype (**Table 1, main manuscript**). Because clinicians must be able to easily find the information, the interpreted phenotype may be documented as a problem list entry or in a patient's summary section; these phenotypes are best stored in the EHR at the "person level" rather than at the date-centric "encounter level". Additionally, results should be entered as standardized and discrete terms to facilitate using them to provide point-of-care CDS (see **G6PD Pre- and Post-Test Alerts and Flow Chart** for example CDS alerts; <https://cpicpgx.org/cpic-guideline-for-g6pd/>) (1).

Because pharmacogenetic test results have lifetime implications and clinical significance, results should be placed into a section of the EHR that is accessible independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. To facilitate this process, CPIC is providing gene-specific information figures and tables that include complete diplotype to phenotype translation tables, diagram(s) that illustrate how *G6PD* pharmacogenetic test results could be entered into an EHR, example EHR consultation/genetic test interpretation language and widely used nomenclature systems (see <https://cpicpgx.org/cpic-guideline-for-g6pd/>) (1, 136).

Point-of-care CDS should be designed to effectively notify clinicians of prescribing implications at any time after the test result is entered into the EHR. CPIC is also providing gene-drug specific tables that provide guidance to achieve these objectives with diagrams that illustrate how point-of-care CDS should be entered into the EHR, example pre- and post-test

alert language, and widely used nomenclature systems for relevant drugs (see <https://cpicpgx.org/cpic-guideline-for-g6pd/> (1)). With respect to this guideline, the CDS language was created for medium and high risk drugs in G6PD deficiency; it is up to individual institutions to determine for which drugs to implement CDS.

TABLE S1. EVIDENCE LINKING G6PD DEFICIENCY TO DRUG-INDUCED HEMOLYSIS

Drug	Type of Experimental Model	Major Findings	References	Level of Evidence
4-Aminosalicylic acid	In vitro	After in vitro incubation with p-aminosalicylic acid, erythrocytes from individuals with G6PD deficiency did NOT exhibit a decline in reduced glutathione concentration or formation of methemoglobinemia.	Hla Pe, <i>et al.</i> (1969) (57)	Moderate
4-Aminosalicylic acid	Clinical	Hemolysis with p-aminosalicylic acid attributed to G6PD deficiency.	Szeinberg, <i>et al.</i> (1957) (58)	Weak
Aspirin	In vitro	Salicylic acid inhibits the pentose phosphate pathway in the erythrocytes of G6PD-deficient subjects in vitro but the degree of inhibition is not sufficient to induce hemolytic anemia following aspirin ingestion.	Worathumrong, <i>et al.</i> (1975) (137)	Moderate
Aspirin	In vitro	Aspirin did NOT cause a decrease in reduced glutathione concentrations in G6PD-deficient erythrocytes.	Sheth, <i>et al.</i> (1981) (138) Ali, <i>et al.</i> (1999) (139)	Moderate
Aspirin \leq 1g/day	Clinical	Individuals with G6PD deficiency did NOT experience hemolysis with aspirin \leq 1g/day.	Shalev (1991) (140) Rigattieri, <i>et al.</i> (2008) (141) Pappas, <i>et al.</i> (2013) (142) Biscaglia, <i>et al.</i> (2015) (143) Kafkas, <i>et al.</i> (2015) (144) Sanna, <i>et al.</i> (2021) (145) Chen, <i>et al.</i> (2021) (146)	Moderate

			Chen, <i>et al.</i> (2021) (147) Campbell, <i>et al.</i> (2007) (148)	
Aspirin >1g /day	Clinical	Hemolysis with aspirin >1g/day attributed to G6PD deficiency.	Szeinberg, <i>et al.</i> (1960) (149) Shahidi, <i>et al.</i> (1970) (150) Brown, <i>et al.</i> (1972) (151) Chan, <i>et al.</i> (1976) (152) Meloni, <i>et al.</i> (1989) (153) Glader, (1976) (154) Seeler, <i>et al.</i> (1984) (155)	Weak
Aspirin - dose unknown	Clinical	Hemolysis with aspirin (unknown dose) attributed to G6PD deficiency.	Westring, <i>et al.</i> (1966) (156) Onadeko, <i>et al.</i> (1974) (157) Herman, <i>et al.</i> (1975) (61) Choudhry, <i>et al.</i> (1990) (63) Khurana, <i>et al.</i> (1998) (158) Hagag, <i>et al.</i> (2018) (159) Ahmed, <i>et al.</i> (1971) (87)	Weak
Chloramphenicol	In vitro	Chloramphenicol decreases the capacity for glutathione reduction by inhibiting hexokinase and glutathione reductase.	Gorodischer, <i>et al.</i> (1972) (160)	Moderate
Chloramphenicol	In vitro	Chloramphenicol caused a significant concentration-dependent decrease in reduced glutathione concentrations in G6PD-deficient erythrocytes when compared to normal erythrocytes.	Ali, <i>et al.</i> (1999) (139)	Moderate
Chloramphenicol	Clinical	Hemolysis with chloramphenicol attributed to G6PD deficiency.	Flatz, <i>et al.</i> (1963) (161) Chatterji, <i>et al.</i> (1963) (162) Hersko, <i>et al.</i> (1967) (59) Rajkondawar, <i>et al.</i> (1968) (78) Forrest, <i>et al.</i> (1969) (163) McCaffrey, <i>et al.</i> (1971) (164) Owusu, <i>et al.</i> (1972) (60)	Weak

			Bakshi, <i>et al.</i> (1972) (165) Herman, <i>et al.</i> (1975) (61) Crowell, <i>et al.</i> (1984) (62) Choudhry, <i>et al.</i> (1990) (63) Choudhry, <i>et al.</i> (1978) (64) Owusu, (1972) (65) La Grutta, <i>et al.</i> (1967) (66) Chan, <i>et al.</i> (1971) (67)	
Chloroquine	In vitro	Chloroquine did NOT generate hydrogen peroxide in human erythrocytes.	Cohen, <i>et al.</i> (1964) (166)	Weak
Chloroquine	Preclinical	A humanized mouse model treated with chloroquine did NOT result in the loss of G6PD-deficient human red blood cells.	Rochford, <i>et al.</i> (2013) (32)	High
Chloroquine	Clinical	Hemolysis with chloroquine attributed to G6PD deficiency.	Dukes, <i>et al.</i> (1968) (167) Choudhry, <i>et al.</i> (1978) (64) Choudhry, <i>et al.</i> (1980) (168) Agarwal, <i>et al.</i> (1985) (169) Stein, <i>et al.</i> (1987) (170) Choudhry, <i>et al.</i> (1990) (63) Kuipers, <i>et al.</i> (2020) (171) Khoo, (1981) (69) Buchachart, <i>et al.</i> (2001) (70) Mandi, <i>et al.</i> (2005) (48) Meissner, <i>et al.</i> (2005) (49)	Weak
Ciprofloxacin	Clinical	Hemolysis with ciprofloxacin attributed to G6PD deficiency.	Kundu, <i>et al.</i> (2000) (94) Sansone, <i>et al.</i> (2010) (95) Andrews, <i>et al.</i> (1999) (96)	Weak

Dapsone	In vitro	Dapsone's hydroxyl metabolite shortens the survival of erythrocytes with G6PD deficiency.	Glader, <i>et al.</i> (1973) (33) Scott, <i>et al.</i> (1973) (34) Grossman, <i>et al.</i> (1995) (172)	Moderate
Dapsone	In vitro	Dapsone's hydroxyl metabolite caused a significant decreased in reduced glutathione concentrations in G6PD-deficient erythrocytes when compared to normal erythrocytes.	Scott, <i>et al.</i> (1973) (34) Magon, <i>et al.</i> (1981) (173) Magon, <i>et al.</i> (1981) (174) Grossman, <i>et al.</i> (1995) (172)	Moderate
Dapsone	Preclinical	A humanized mouse model treated with dapsone resulted in the loss of G6PD-deficient human red blood cells comparable to primaquine.	Rochford, <i>et al.</i> (2013) (32)	High
Dapsone	Clinical	Hemolysis and methemoglobinemia with dapsone attributed to G6PD deficiency.	Degowin, <i>et al.</i> (1966) (175) McNamara, <i>et al.</i> (1966) (176) Carson, (1968) (177) Lewis, <i>et al.</i> (1969) (178) Willerson, <i>et al.</i> (1972) (29) Rasbridge, <i>et al.</i> (1973) (30) Onadeko, <i>et al.</i> (1974) (157) Ponnampalam, <i>et al.</i> (1981) (179) Byrd, <i>et al.</i> (1991) (180) Todd, <i>et al.</i> (1994) (181) Allouche, <i>et al.</i> (2004) (182) Draelos, <i>et al.</i> (2007) (27) Fanello, <i>et al.</i> (2008) (183) Piette, <i>et al.</i> (2008) (28) Premji, <i>et al.</i> (2009) (184) Tiono, <i>et al.</i> (2009) (185) Serpa, <i>et al.</i> (2010) (31) Dunyo, <i>et al.</i> (2011) Van Malderen, <i>et al.</i> (2012) (186)	High

			Pamba, <i>et al.</i> (2012) (126) Ghatak, <i>et al.</i> (2013) (41) Poirot, <i>et al.</i> (2015) (187) Murphy, <i>et al.</i> (2016) (188)	
Dimercaprol	Clinical	Hemolysis with dimercaprol attributed to G6PD deficiency.	Janakiraman, <i>et al.</i> (1978) (76)	Weak
Doxorubicin	In vitro	After in vitro incubation with doxorubicin, erythrocytes from individuals with G6PD deficiency exhibited oxidative stress.	Sagone, <i>et al.</i> (1979) (189) Shinohara, <i>et al.</i> (1980) (190)	Weak
Doxorubicin	Clinical	Hemolysis with doxorubicin attributed to G6PD deficiency.	Doll, <i>et al.</i> (1983) (191) Chung, <i>et al.</i> (2019) (77)	Weak
Furazolidone	Clinical	Hemolysis with furazolidone attributed to G6PD deficiency.	Rajkondawar, <i>et al.</i> (1968) (78) Herman, <i>et al.</i> (1975) (61)	Weak
Glyburide	Clinical	Hemolysis with glyburide attributed to G6PD deficiency.	Meloni, <i>et al.</i> (1996) (79) Vinzio, <i>et al.</i> (2004) (80) Carette, <i>et al.</i> (2011) (81)	Weak
Hydroxychloroquine	Clinical	Hemolysis with hydroxychloroquine attributed to G6PD deficiency.	Beauverd, <i>et al.</i> (2020) (192) Maillart, <i>et al.</i> (2020) (193) Mohammad, <i>et al.</i> (2018) (71) Sasi, <i>et al.</i> (2020) (194) Abramova, <i>et al.</i> (2020) (72) Mastroianni, <i>et al.</i> (2020) (195) Chaney, <i>et al.</i> (2020) (196) Ramirez de Oleo, <i>et al.</i> (2020) (73) Zuchelkowski, <i>et al.</i> (2020) (74) Aguilar, <i>et al.</i> (2020) (197) Sgherza, <i>et al.</i> (2020) (75) Laslett, <i>et al.</i> (2021) (198)	Weak

Mafenide	Clinical	Hemolysis with mafenide attributed to G6PD deficiency.	Marsicano, <i>et al.</i> (1973) (82)	Weak
Methylene blue	In vitro	Methylene blue elevates the activity of the hexose monophosphate shunt in erythrocytes.	Baird, <i>et al.</i> (1986) (199) Baird, <i>et al.</i> (1986) (200)	Moderate
Methylene blue	In vitro	The rate of oxidation of glutathione by direct reaction with methylene blue was equivalent in normal and G6PD deficient erythrocytes.	Kelner, <i>et al.</i> (1986) (201)	Weak
Methylene blue	Clinical	Hemolysis and methemoglobinemia with methylene blue attributed to G6PD deficiency.	Rosen, <i>et al.</i> (1971) (36) Bilgin, <i>et al.</i> (1998) (202) Gauthier (2000) (42) Karadsheh, <i>et al.</i> (2001) (39) Liao, <i>et al.</i> (2002) (203) Janssen, <i>et al.</i> (2004) (204) Maddali, <i>et al.</i> (2005) (43) Foltz, <i>et al.</i> (2006) (40) Mullick, <i>et al.</i> (2007) (37) Muller, <i>et al.</i> (2013) (127) Ghatak, <i>et al.</i> (2013) (41) Bucklin, <i>et al.</i> (2013) (45) Khanal, <i>et al.</i> (2015) (205) Ibrahim, <i>et al.</i> (2018) (46) Balwani, <i>et al.</i> (2017) (38) Benchamol, <i>et al.</i> (2018) (44) Raru, <i>et al.</i> (2019) (47) Golden, <i>et al.</i> (1998) (206) Mandi, <i>et al.</i> (2005) (48) Meissner, <i>et al.</i> (2005) (49)	Moderate

Nalidixic acid	Clinical	Hemolysis with nalidixic acid attributed to G6PD deficiency.	Mandal, <i>et al.</i> (1970) (98) Alessio, <i>et al.</i> (1972) (99)	Weak
Nitrofurantoin	Clinical	Hemolysis with nitrofurantoin attributed to G6PD deficiency.	Garrett, <i>et al.</i> (1963) (108) Pritchard, <i>et al.</i> (1965) (207) Herman, <i>et al.</i> (1975) (61) Lavelle, <i>et al.</i> (1976) (208) Chan, <i>et al.</i> (1976) (152) Gait (1990) (209) Ghimire, <i>et al.</i> (2013) (86) Van de Mheen, (2014) (210) Hagag, <i>et al.</i> (2018) (159)	Moderate
Norfloxacin	Clinical	Hemolysis and methemoglobinemia with norfloxacin attributed to G6PD deficiency.	Sharma, <i>et al.</i> (2017) (97)	Weak
Ofloxacin	Clinical	Individuals with G6PD deficiency did NOT experience hemolysis with ofloxacin.	Watson, <i>et al.</i> (2018) (100)	Weak
Pegloticase	Clinical	Hemolysis and methemoglobinemia with pegloticase attributed to G6PD deficiency.	Geraldino-Pardillia, <i>et al.</i> (2014) (211) Owens, <i>et al.</i> (2016) (212) Adashek, <i>et al.</i> (2018) (213) Minshar, <i>et al.</i> (2019) (214)	High
Phenazopyridine	Clinical	Hemolysis with phenazopyridine attributed to G6PD deficiency.	Mercieca, <i>et al.</i> (1982) (83) Tishler, <i>et al.</i> (1983) (84) Galun, <i>et al.</i> (1987) (85) Ghimire, <i>et al.</i> (2013) (86)	Weak
Primaquine - low dose for Plasmodium falciparum malaria	Clinical	A single low dose (0.25 mg/kg) of primaquine used as a gametocytocide for the treatment of Plasmodium	Pett, <i>et al.</i> (2019) (215) Raman, <i>et al.</i> (2019) (216) Dysoley, <i>et al.</i> (2019) (217) Graves, <i>et al.</i> (2018) (218) Chen, <i>et al.</i> (2018) (219)	High

		falciparum malaria is generally safe in patients with G6PD deficiency.	Bastiaens, <i>et al.</i> (2018) (220) Tine, <i>et al.</i> (2017) (221) Wickham, <i>et al.</i> (2016) (222) Mwaiswelo, <i>et al.</i> (2016) (223) Bancone, <i>et al.</i> (2016) (224)	
Primaquine - low dose for Plasmodium vivax malaria	Clinical	An intermittent dosing regimen of 0.75 mg/kg or 45 mg once weekly for 8 weeks for the treatment of Plasmodium vivax malaria is generally safe with monitoring in patients with G6PD deficiency.	Taylor, <i>et al.</i> (2019) (225) Saravu, <i>et al.</i> (2016) (226) Kheng, <i>et al.</i> (2015) (227) Myat Phone, <i>et al.</i> (1994) (92) Alving, <i>et al.</i> (1960) (228) Tang, <i>et al.</i> (2021) (229)	High
Primaquine - standard dose	Clinical	Hemolysis with standard doses of primaquine attributed to G6PD deficiency.	Bancone, <i>et al.</i> (2021) (10)	High
Quinine	In vitro	There is no significant effect of quinine on hemolysis risk, glutathione levels and methemoglobin values in erythrocytes from patients with G6PD deficiency compared to normal erythrocytes.	Bennett, <i>et al.</i> (1967) (93)	Moderate
Quinine	Clinical	Hemolysis with quinine attributed to G6PD deficiency.	Ahmed, <i>et al.</i> (1971) (87) Glass, <i>et al.</i> (1973) (88) Dash, <i>et al.</i> (1977) (89) Tran, <i>et al.</i> (1996) (91) Bichali, <i>et al.</i> (2017) (90) Myat Phone, <i>et al.</i> (1994) (92)	Weak
Rasburicase	Clinical	Hemolysis and methemoglobinemia with rasburicase attributed to G6PD deficiency.	Sonbol, <i>et al.</i> (2013) (230) Zaramella, <i>et al.</i> (2013) (231) Cheah, <i>et al.</i> (2013) (232) Pansy, <i>et al.</i> (2014) (233) Pansy, <i>et al.</i> (2014) (234)	High

			<p>Bucklin, <i>et al.</i> (2013) (45) Yeh, <i>et al.</i> (2014) (235) Roberts, <i>et al.</i> (2015) (236) Bontant, <i>et al.</i> (2014) (237) Zhang, <i>et al.</i> (2014) (238) Dasararaju, <i>et al.</i> (2015) (239) Oluwasanjo, <i>et al.</i> (2015) (240) Sherwood, <i>et al.</i> (2016) (241) Montgomery, <i>et al.</i> (2017) (242) Reeves, <i>et al.</i> (2016) (243) Khan, <i>et al.</i> (2017) (244) Ibrahim, <i>et al.</i> (2018) (46) Cooling (2017) (245) Akande, <i>et al.</i> (2017) (246) Younis, <i>et al.</i> (2018) (247) Ferguson, <i>et al.</i> (2018) (248) Robinson, <i>et al.</i> (2019) (249) Raru, <i>et al.</i> (2019) (47) Bachmann, <i>et al.</i> (2019) (250) Friedman, <i>et al.</i> (2020) (251) Cabantous, <i>et al.</i> (2020) (252) Pirrone, <i>et al.</i> (2021) (253) Madanat, <i>et al.</i> (2021) (254)</p>	
Sulfadiazine	Clinical	Hemolysis with sulfadiazine attributed to G6PD deficiency.	<p>Eldad, <i>et al.</i> (1991) (103) Rajkondawar, <i>et al.</i> (1968) (78) Szeinberg, <i>et al.</i> (1959) (102)</p>	Weak
Sulfadimidine	Ex vivo	Erythrocytes from individuals with G6PD deficiency who took sulfadimidine exhibited a decline of reduced glutathione concentration.	<p>Woolhouse, <i>et al.</i> (1982) (104)</p>	Weak

Sulfamethoxazole	Clinical	Hemolysis with sulfamethoxazole attributed to G6PD deficiency.	Allen, <i>et al.</i> (1972) (255) Owusu, <i>et al.</i> (1972) (65) Chan, <i>et al.</i> (1974) (256) Chan, <i>et al.</i> (1976) (152) Danielson, <i>et al.</i> (1984) (257) Calabro, <i>et al.</i> (1989) (258) Reinke, <i>et al.</i> (1995) (259) Tungsiripat, <i>et al.</i> (2008) (260) Chisholm-Burns, <i>et al.</i> (2010) (261) Serpa, <i>et al.</i> (2010) (31) Perdigones, <i>et al.</i> (2014) (262) Hagag, <i>et al.</i> (2018) (159) Chan, <i>et al.</i> (1975) (263) Markowitz, <i>et al.</i> (1987) (264) Hui, <i>et al.</i> (2006) (265) Lu, <i>et al.</i> (2020) (266)	Weak
Sulfanilamide	In vitro	Sulfanilamide caused a significant concentration-dependent decrease in reduced glutathione concentrations in G6PD-deficient erythrocytes when compared to normal erythrocytes.	Ali, <i>et al.</i> (1999) (139) Szeinberg, <i>et al.</i> (1959) (102)	Weak
Sulfanilamide	Clinical	Hemolysis with sulfanilamide attributed to G6PD deficiency.	La Grutta, <i>et al.</i> (1967) (66) Richardson, <i>et al.</i> (1969) (105)	Weak
Sulfasalazine	Clinical	Hemolysis with sulfasalazine attributed to G6PD deficiency.	Cohen, <i>et al.</i> (1968) (101)	Weak
Sulfisoxazole	Clinical	Hemolysis with sulfisoxazole attributed to G6PD deficiency.	Garrett, <i>et al.</i> (1963) (108) Perkins (1971) (107) Meister, <i>et al.</i> (1975) (106) Heinrich, <i>et al.</i> (1971) (109)	Weak
Tafenoquine	Preclinical	A humanized mouse model treated with tafenoquine resulted in the loss of	Rochford, <i>et al.</i> (2013) (32)	High

		G6PD-deficient human red blood cells comparable to primaquine.		
Tafenoquine	Clinical	Hemolysis with tafenoquine attributed to G6PD deficiency.	Rueangweerayut, <i>et al.</i> (2017) (50)	High
Tafenoquine	Clinical	Tafenoquine is not associated with excess hemolysis in patients with normal G6PD activity (defined as $\geq 70\%$ normal activity).	Llanos-Cuentas, <i>et al.</i> (2019) (52) Lacerda, <i>et al.</i> (2019) (51)	Moderate
Tolbutamide	Clinical	Hemolysis with tolbutamide attributed to G6PD deficiency.	Pavlic, <i>et al.</i> (1966) (110) Cseoreghy, <i>et al.</i> (1988) (111)	Weak
Toluidine blue	Clinical	Hemolysis and methemoglobinemia with toluidine blue attributed to G6PD deficiency.	Teunis, <i>et al.</i> (1970) (55)	Weak
Vitamin C	In vitro	Incubation of erythrocytes with vitamin C induced hemolysis, which was exacerbated by G6PD deficiency.	Zhang, <i>et al.</i> (2016) (267)	Weak
Vitamin C	Clinical	Hemolysis with high doses of vitamin C, and not therapeutic doses, attributed to G6PD deficiency.	Lee, <i>et al.</i> (2017) (9) Reeves, <i>et al.</i> (2016) (243) Allister, <i>et al.</i> (2017) (268) Khan, <i>et al.</i> (2017) (244) Quinn, <i>et al.</i> (2017) (112) Balwani, <i>et al.</i> (2017) (38) Rehman, <i>et al.</i> (2018) (269) Rees, <i>et al.</i> (2018) (113) Raru, <i>et al.</i> (2019) (47) Lo, <i>et al.</i> (2020) (270) Eskandarani, <i>et al.</i> (2020) (271) Visclosky, <i>et al.</i> (2021) (272) Tang, <i>et al.</i> (2021) (229)	Weak

Vitamin K	Clinical	Individuals with G6PD deficiency did NOT experience hemolysis with vitamin K.	Lee, <i>et al.</i> (2017) (9)	Moderate
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TABLE S2. ASSOCIATION BETWEEN ALLELIC VARIANTS AND G6PD ACTIVITY AS DEFINED BY THE WORLD HEALTH ORGANIZATION

Functional Status	Allele Classification
Severe enzyme deficiency, <10% normal enzyme activity, with associated chronic non-spherocytic hemolytic anemia	WHO Class I
Severe enzyme deficiency, <10% normal enzyme activity, no chronic non-spherocytic hemolytic anemia	WHO Class II
Moderate to mild deficiency, 10-60% of normal enzyme activity	WHO Class III
Normal activity, 60-150% normal enzyme activity	WHO Class IV

WHO, World Health Organization. The WHO is proposing a new classification system: Meeting report of the technical consultation to review the classification of glucose-6-phosphate dehydrogenase (G6PD). < <https://www.who.int/publications/m/item/WHO-UCN-GMP-MPAG-2022.01>> (2022). Accessed April 21 2022.

References: (2, 115)

Note: A single case of increased activity (a putative “Class V” allele) was previously included but will not be included going forward.

TABLE S3. SUMMARY OF SELECT REGULATORY AGENCY WARNINGS FOR MEDICATION USE IN PATIENTS WITH G6PD DEFICIENCY

	United States Food and Drug Administration (FDA)	European Medicines Agency (EMA)	Pharmaceuticals and Medical Devices Agency - Japan (PMDA)	Health Canada (Santé Canada) (HCSC)
4-aminosalicylic acid	n/a	n/a	n/a	n/a
aspirin	n/a	n/a	n/a	n/a
chloramphenicol	n/a	n/a	n/a	n/a
chloroquine	CAUTION	n/a	n/a	n/a
chlorpropamide	CAUTION	n/a	n/a	CAUTION
ciprofloxacin	n/a	n/a	n/a	n/a
dabrafenib	CAUTION	n/a	n/a	n/a
dapsone	AVOID	n/a	CAUTION	CAUTION
dimercaprol	n/a	n/a	n/a	n/a
doxorubicin	n/a	n/a	n/a	n/a
furazolidone	n/a	n/a	n/a	n/a
gliclazide	n/a	n/a	n/a	n/a
glimepiride	CAUTION	CAUTION	n/a	CAUTION
glipizide	CAUTION	n/a	n/a	n/a
glyburide	CAUTION	AVOID	n/a	CAUTION
hydroxychloroquine	CAUTION	n/a	n/a	n/a
mafenide	CAUTION	n/a	n/a	n/a
mepacrine	n/a	n/a	n/a	n/a
mesalazine	n/a	n/a	n/a	n/a
methylene blue	AVOID	AVOID	CAUTION	n/a
moxifloxacin	n/a	n/a	n/a	n/a
nalidixic acid	CAUTION	n/a	CAUTION	n/a
nicorandil	n/a	n/a	n/a	n/a
nitrofurantoin	CAUTION	n/a	n/a	CAUTION

norfloxacin	CAUTION	n/a	n/a	CAUTION
ofloxacin	n/a	n/a	n/a	n/a
pegloticase	AVOID	AVOID	n/a	n/a
phenazopyridine	n/a	n/a	n/a	n/a
primaquine	AVOID	n/a	n/a	CAUTION
probenecid	CAUTION	n/a	n/a	n/a
quinine	CAUTION	n/a	n/a	AVOID
rasburicase	AVOID	AVOID	AVOID	AVOID
sodium nitrite	AVOID	n/a	n/a	AVOID
sulfacetamide	n/a	n/a	n/a	n/a
sulfadiazine	CAUTION	n/a	CAUTION	CAUTION
sulfadimidine	n/a	n/a	n/a	n/a
sulfamethoxazole	CAUTION	n/a	AVOID	CAUTION
sulfanilamide	n/a	n/a	n/a	n/a
sulfasalazine	CAUTION	n/a	CAUTION	CAUTION
sulfisoxazole	CAUTION	n/a	n/a	AVOID
tafenoquine	AVOID	n/a	n/a	n/a
tolazamide	CAUTION	n/a	n/a	n/a
tolbutamide	CAUTION	n/a	n/a	CAUTION
toluidine blue	n/a	n/a	n/a	n/a
trametinib	CAUTION	n/a	n/a	n/a
vitamin C	CAUTION	n/a	CAUTION	CAUTION
vitamin K	n/a	n/a	n/a	n/a

Data in the table and in the text below were extracted from PharmGKB (www.pharmgkb.org) and is current as of March 2022. For the most up-to-date regulatory agency warnings, refer to PharmGKB (<https://www.pharmgkb.org/labelAnnotations>).

n/a = not applicable (i.e., G6PD-related information is not mentioned in regulatory agency prescribing information or the drug is not available in the particular region with regulatory agency oversight)

Caution

- Chloroquine (FDA): “Chloroquine may cause hemolysis in glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. Blood monitoring may be needed as hemolytic anemia may occur, in particular in association with other drugs that cause hemolysis.”
- Chlorpropamide (FDA): “Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Because DIABINESE belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered.”
- Chlorpropamide (HCSC): “Hemolytic anemia: Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Because APO-CHLORPROPAMIDE belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered. In post-marketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.”
- Dabrafenib (FDA): “TAFINLAR, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Monitor patients with G6PD deficiency for signs of hemolytic anemia while taking TAFINLAR.”
- Dapsone (PMDA): “Patients with a glucose-6-phosphate dehydrogenase deficiency (hemolysis may occur).”
- Dapsone (HCSC): “Oral dapsone treatment has produced dose-related hemolysis and hemolytic anemia. Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more prone to hemolysis with the use of certain drugs. G6PD deficiency is most prevalent in populations of African, South Asian, Middle Eastern, and Mediterranean ancestry... “In patients treatment with ACZONE, including patients who were G6PD deficient, there was no evidence of clinically relevant hemolysis or anemia. A randomized, double-blind, vehicle-controlled, cross-over clinical study was conducted in G6PD-deficient patients with acne vulgaris to evaluate the risk of hemolysis and/or hemolytic anemia with ACZONE treatment. In this study 56 safety-evaluable patients showed no evidence of clinically relevant hemolysis or anemia. Some subjects with G6PD deficiency using ACZONE developed laboratory changes suggestive of mild hemolysis.”
- Glimepiride (FDA): “Hemolytic Anemia: Sulfonylureas can cause hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Because AMARYL is a sulfonylurea, use caution in patients with G6PD deficiency and consider the use of a non-sulfonylurea alternative.”
- Glimepiride (EMA): “Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to haemolytic anaemia. Since glimepiride belongs to the chemical class of sulfonylurea medicinal products, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.”
- Glimepiride (HCSC): “Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to hemolytic anemia. Since AMARYL belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a nonsulfonylurea alternative should be considered.”
- Glipizide (FDA): “Hemolytic Anemia: Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Because GLUCOTROL belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered.”
- Glyburide (FDA): “Hemolytic Anemia: Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Because GLYNASE PresTab belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered. In post

marketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.”

- Glyburide (HCSC): “Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD)-deficiency with sulfonylurea agents can lead to hemolytic anemia. Since glyburide belongs to this class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a nonsulfonylurea alternative should be considered.”
- Hydroxychloroquine (FDA): “Hemolytic Anemia Associated with G6PD Deficiency: Hemolysis has been reported in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Monitor for hemolytic anemia as this can occur, particularly in association with other drugs that cause hemolysis.”
- Mafenide (FDA): “Fatal hemolytic anemia with disseminated intravascular coagulation, presumably related to a glucose-6-phosphate dehydrogenase deficiency, has been reported following therapy with mafenide acetate.”
- Methylene Blue (PDMA): “Patients with known glucose-6-phosphate dehydrogenase deficiency: Exacerbation of methemoglobinemia and hemolysis may occur... When exacerbation of methemoglobinemia or hemolysis occurs following the administration of this product, glucose-6-phosphate dehydrogenase deficiency, NADPH reductase deficiency or overdosing is suspected. Monitor patients closely, and consider discontinuation of the product or switch to different therapies if these signs develop.”
- Nitrofurantoin (FDA): “Cases of hemolytic anemia of the primaquine-sensitivity type have been induced by nitrofurantoin. Hemolysis appears to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients. This deficiency is found in 10 percent of Blacks and a small percentage of ethnic groups of Mediterranean and Near-Eastern origin. Hemolysis is an indication for discontinuing Furadantin; hemolysis ceases when the drug is withdrawn.”
- Nitrofurantoin (HCSC): “Cases of hemolytic anemia of the primaquine sensitivity type have been induced by nitrofurantoin. The hemolysis appears to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients. This deficiency is found in 10% of blacks and a small percentage of ethnic groups of Mediterranean and Near-Eastern origin. Any sign of hemolysis is an indication to discontinue the drug. Hemolysis ceases when the drug is withdrawn... Nitrofurantoin has been detected in trace amounts in breast milk. Caution should be exercised when nitrofurantoin is administered to a nursing woman, especially if the infant is known or suspected to have a glucose-6-phosphate dehydrogenase deficiency.”
- Norfloxacin (FDA): “Rarely, hemolytic reactions have been reported in patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity who take quinolone antibacterial agents, including norfloxacin (see ADVERSE REACTIONS)... Adverse Reactions...Hematologic: Neutropenia; leukopenia, agranulocytosis; hemolytic anemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency...”
- Norfloxacin (HCSC): “Rarely, hemolytic reactions have been reported in patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity who take quinolone antibacterial agents, including norfloxacin.”
- Primaquine (HCSC): “Observe particular caution in individuals with a personal or family history of favism, hemolytic anemia, or glucose-6-phosphate dehydrogenase (G-6-PD) deficiency...Adverse effects...Hematologic: Leukopenia, hemolytic anemia especially in G-6-PD deficient individuals and methemoglobinemia especially in NADH methemoglobin reductase deficient individuals.”
- Probenecid (FDA): “Adverse Reactions...Hematologic: aplastic anemia, leukopenia, hemolytic anemia which in some patients could be related to genetic deficiency of glucose-6-phosphate dehydrogenase in red blood cells, anemia.”

- Quinine (FDA): “Acute hemolytic anemia has been reported in patients receiving quinine for treatment of malaria, including patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. The cause for the acute hemolytic anemia in quinine-treated patients with malaria and its potential relationship with G6PD deficiency has not been determined. Closely monitor hemoglobin and hematocrit during quinine treatment. Quinine should be discontinued if patients develop acute hemolytic anemia.”
- Sulfadiazine (FDA): “The use of SILVADENE Cream 1% (silver sulfadiazine) in some cases of glucose-6-phosphate dehydrogenase-deficient individuals may be hazardous, as hemolysis may occur.”
- Sulfadiazine (PMDA): “Precautions...Patients with a glucose-6-phosphate dehydrogenase (G-6-PD) deficiency (hemolysis may occur).”
- Sulfadiazine (HCSC): “Silver sulfadiazine cream should be used with caution on patients with a history of glucose-6-phosphate dehydrogenase deficiency as hemolysis may occur.”
- Sulfamethoxazole/trimethoprim (FDA): “In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. This reaction is frequently dose-related.”
- Sulfamethoxazole/trimethoprim (HCSC): “In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. This reaction is frequently dose-related.”
- Sulfasalazine (FDA): “Patients with glucose-6-phosphate dehydrogenase deficiency should be observed closely for signs of hemolytic anemia. This reaction is frequently dose related. If toxic or hypersensitivity reactions occur, the drug should be discontinued immediately.”
- Sulfasalazine (PMDA): “Precautions...Patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency (hemolysis may occur).”
- Sulfasalazine (HCSC): “Patients, especially those with glucose-6-phosphate dehydrogenase deficiency, should be observed closely for signs of hemolytic anemia. This reaction is frequently dose related. If toxic or hypersensitivity reactions occur, the drug should be discontinued immediately...Caution should be used, particularly if breastfeeding premature infants or those deficient in Glucose-6-Phosphate Dehydrogenase (G-6-PD).
- Sulfisoxazole (FDA): “In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur; this reaction is frequently dose related.”
- Tolazamide (FDA): “Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with sulfonyleurea agents can lead to hemolytic anemia. Because tolazamide belongs to the class of sulfonyleurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonyleurea alternative should be considered. In post-marketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.”
- Tolbutamide (FDA): “Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with sulfonyleurea agents can lead to hemolytic anemia. Because tolbutamide belongs to the class of sulfonyleurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonyleurea alternative should be considered. In post-marketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.”
- Tolbutamide (HCSC): “Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with sulfonyleurea agents can lead to hemolytic anemia. Because APO-TOLBUTAMIDE belongs to the class of sulfonyleurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonyleurea alternative should be considered. In post marketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.”
- Trametinib (FDA): “The trials excluded patients with abnormal left ventricular ejection fraction, history of acute coronary syndrome within 6 months, history of Class II or greater congestive heart failure (New York Heart Association)... or known history of G6PD deficiency.”
- Vitamin C (FDA): “Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. Since MoviPrep contains sodium ascorbate and ascorbic acid, MoviPrep should be used with caution in patients

with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, especially G-6-PD deficiency patients with active infection, with a history of hemolysis, or taking concomitant medications known to precipitate hemolytic reactions.”

- Vitamin C (PMDA): “Precautions...Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency (hemolysis may occur).”
- Vitamin C (HCSC): “Ascorbic acid: Patients with Glucose-6-phosphate dehydrogenase deficiency may be at risk of acute haemolysis due to the presence of ascorbate.”

Avoid

- Dapsone (FDA): “Cases of methemoglobinemia, with resultant hospitalization, have been reported postmarketing in association with ACZONE Gel, 5% treatment. Patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methemoglobinemia are more susceptible to drug-induced methemoglobinemia. Avoid use of ACZONE Gel, 5% in those patients with congenital or idiopathic methemoglobinemia...Oral dapsone treatment has produced dose-related hemolysis and hemolytic anemia. Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more prone to hemolysis with the use of certain drugs. G6PD deficiency is most prevalent in populations of African, South Asian, Middle Eastern, and Mediterranean ancestry... Some subjects with G6PD deficiency using ACZONE Gel developed laboratory changes suggestive of hemolysis. There was no evidence of clinically relevant hemolysis or anemia in patients treated with ACZONE Gel, 5%, including patients who were G6PD deficient...Orally administer dapsone appears in human milk and could result in hemolytic anemia and hyperbilirubinemia especially in infants with G6PD deficiency.”
- Glyburide (EMA): “In patients carrying a G6PD enzyme deficiency, cases of acute haemolytic anaemia have been reported with glibenclamide. It should therefore not be prescribed for these patients, and the use of an alternative treatment is strongly recommended, if available. If there is no alternative, the decision for each patient must consider the danger of haemolysis and the potential benefit expected from the treatment. If it is necessary to prescribe this medicinal product, screening should be conducted for the occurrence of any haemolysis.”
- Methylene Blue (FDA): “Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with PROVAYBLUE® may result in severe hemolysis and severe anemia. PROVAYBLUE® is contraindicated for use in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.”
- Methylene Blue (EMA): “Contraindications...Patients with Glucose-6-phosphate dehydrogenase deficiency (G6PD) due to the risk of haemolytic anaemia...”
- Pegloticase (FDA): “Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. Do not administer KRYSTEXXA to patients with G6PD deficiency...Life threatening hemolytic reactions and methemoglobinemia have been reported with KRYSTEXXA in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency...Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. For example, patients of African, Mediterranean (including Southern European and Middle Eastern), and Southern Asian ancestry are at increased risk for G6PD deficiency.”
- Pegloticase (EMA): “Contraindications: Glucose-6-phosphate dehydrogenase (G6PD) deficiency and other cellular metabolic disorders known to cause haemolysis and methemoglobinemia. All patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) should be screened for G6PD deficiency before starting KRYSTEXXA.”
- Primaquine (FDA): “Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing has to be performed before using primaquine. Due to the limitations of 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...Primaquine should not be prescribed

for patients with severe G6PD deficiency...In case of mild to moderate G6PD deficiency, a decision to prescribe primaquine must be based on an assessment of the risks and benefits...When the G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits..."

- Quinine (HCSC): "Contraindications...patients with G-6-PD deficiency... Patients at risk for G-6-PD deficiency should not be breastfed until this disease can be ruled out."
- Rasburicase (FDA): "Do not administer Elitek to patients with glucose-6-phosphate (G6PD) deficiency. Immediately and permanently discontinue Elitek in patients developing hemolysis. Screen patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting Elitek...Elitek 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 Elitek; severe hemolytic reactions occurred within 2-4 days of the start of Elitek."
- Rasburicase (EMA): "Contraindications...G6PD deficiency and other cellular metabolic disorders known to cause haemolytic anaemia...In clinical trials, haematological disorders such as haemolysis, haemolytic anaemia and methaemoglobinemia are uncommonly caused by Fasturtec. The enzymatic digestion of uric acid to allantoin by rasburicase produces hydrogen peroxide and haemolytic anaemia or methaemoglobinaemia have been observed in certain at risk populations such as those with G6PD deficiency."
- Rasburicase (PMDA): "In overseas clinical studies, severe hemolytic anemia was reported in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Patients should be carefully screened for a family history of G6PD deficiency and other red blood cell enzyme defects...Contraindication...Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency or patients with other types of red blood cell enzyme defects that are known to cause hemolytic anemia."
- Rasburicase (HCSC): "FASTURTEC administered to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency can cause severe hemolysis. Therefore, FASTURTEC is contraindicated in individuals deficient in glucose-6-phosphate dehydrogenase (G6PD), in order to prevent hemolytic anemia in this patient population...It is recommended that patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) be screened prior to starting FASTURTEC therapy."
- Sodium Nitrite (FDA): "Because patients with G6PD deficiency are at increased risk of a hemolytic crisis with sodium nitrite administration, alternative therapeutic approaches should be considered in these patients. Patients with known or suspected G6PD deficiency should be monitored for an acute drop in hematocrit. Exchange transfusion may be needed for patients with G6PD deficiency who receive sodium nitrite."
- Sodium Nitrite (HCSC): "Because patients with G6PD deficiency are at increased risk of a hemolytic crisis with sodium nitrite administration, alternative therapeutic approaches should be considered in these patients. Patients with known or suspected G6PD deficiency should be monitored for an acute drop in hematocrit. Exchange transfusion may be needed for patients with G6PD deficiency who receive sodium nitrite."
- Sulfamethoxazole/trimethoprim (PMDA): "Contraindications...Patients with a glucose-6-phosphate dehydrogenase (G-6-PD) deficiency (hemolysis may occur)."
- Sulfisoxazole (HCSC): "PEDIAZOLE® (erythromycin ethylsuccinate and sulfisoxazole acetyl or oral suspension USP) is contraindicated in: uremic patients, and patients with a deficiency of erythrocytic glucose-6-phosphate dehydrogenase (G-6-PD)...Hemolysis may occur in glucose-6-phosphate dehydrogenase deficient individuals."
- Tafenoquine (FDA): "Hemolytic Anemia – Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing must be performed before prescribing ARAKODA [see Contraindications]. 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 ARKODA is contraindicated in patients with G6PD deficiency or unknown G6PD status [see Contraindications]. In clinical trials, declines in hemoglobin levels were reported in some G6PD-normal patients [see Adverse Reactions]. Monitor patients for clinical signs or symptoms of hemolysis [see Warnings and Precautions]. Advise patients to discontinue ARKODA and seek medical attention if signs of hemolysis occur.”

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