PRESCRIBING INFORMATION

PrQuinine-ODAN200 mg Capsules
PrQuinine-ODAN 300 mg Capsules and
PrQuinine-ODAN 300 mg Tablets
quinine sulfate

PART I: HEALTH CARE PRACTITIONER INFORMATION

SUMMARY PRODUCT INFORMATION

INDICATIONS AND CLINICAL USE

Quinine-ODAN (quinine sulfate) is indicated (in combination with a second anti-malarial drug) for the treatment of uncomplicated *Plasmodium falciparum* malaria. Quinine sulfate has been shown to be effective in geographical regions where resistance to chloroquine has been documented.

Geriatrics (≥ 65 years of age):
Reported clinical experience has not identified differences in responses between the elderly and younger patients.

Pediatrics (< 16 years of age):
Quinine is considered acceptable for use in children at doses recommended for the treatment of malaria.

CONTRAINDICATIONS

• Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the prescribing information.
- Hypersensitivity reactions include, but are not limited to the following [*see Warnings and Precautions*]:
  • Thrombocytopenia
  • Idiopathic thrombocytopenia purpura (ITP) and Thrombotic thrombocytopenic purpura (TTP)
  • Hemolytic uremic syndrome (HUS)
  • Blackwater fever (acute intravascular hemolysis, hemoglobinuria, and hemoglobinemia)

  Quinine-ODAN is also contraindicated in patients with the following:
- Prolongation of QT interval
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Myasthenia gravis
- Known hypersensitivity to quinine, mefloquine, or quinidine
- Optic neuritis

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Quinine-ODAN use for the treatment or prevention of nocturnal leg cramps may result in serious and life-threatening hematologic reactions, including thrombocytopenia and hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP). Chronic renal impairment associated with the development of TTP has been reported. The risk associated with quinine sulfate use in the absence of evidence of its effectiveness in the treatment or prevention of nocturnal leg cramps outweighs any potential benefit (see WARNINGS - General).

General

Quinine sulphate is not approved for:

- Treatment of severe or complicated *P. falciparum* malaria.
- Prevention of malaria.
- Treatment or prevention of nocturnal leg cramps.

Use of Quinine-ODAN for Treatment or Prevention of Nocturnal Leg Cramps

Quinine-ODAN may cause unpredictable serious and life-threatening hematologic reactions including thrombocytopenia and hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP) in addition to hypersensitivity reactions, QT prolongation, serious cardiac arrhythmias including torsades de pointes, and other serious adverse events requiring medical intervention and hospitalization. Chronic renal impairment associated with the development of TTP, and fatalities have also been reported. The risk associated with the use of Quinine-ODAN in the absence of evidence of its effectiveness for treatment or prevention of nocturnal leg cramps, outweighs any potential benefit in treating and/or preventing this benign, self-limiting condition [*see Contraindications]*.

Cardiovascular

QT Prolongation and Ventricular Arrhythmias

QT interval prolongation has been a consistent finding in studies which evaluated electrocardiographic changes with oral or parenteral quinine administration, regardless of age, clinical status, or severity of disease. The maximum increase in QT interval has been shown to correspond with peak quinine plasma concentration. Quinine sulfate has been rarely associated with potentially fatal cardiac arrhythmias, including torsades de pointes, and ventricular fibrillation.

Quinine-ODAN is not recommended for use with other drugs known to cause QT prolongation, including Class IA antiarrhythmic agents (e.g., quinidine, procainamide, disopyramide), and Class III antiarrhythmic agents (e.g., amiodarone, sotalol, dofetilide).

The use of macrolide antibiotics such as erythromycin should be avoided in patients receiving Quinine-ODAN. Fatal torsades de pointes was reported in an elderly patient who received concomitant quinine, erythromycin, and dopamine. Although a causal

relationship between a specific drug and the arrhythmia was not established in this case, erythromycin is a CYP3A4 inhibitor and could potentially increase quinine plasma levels when used concomitantly.
Quinine may inhibit the metabolism of certain drugs that are CYP3A4 substrates and are known to cause QT prolongation, e.g., astemizole, cisapride, terfenadine, pimozide, halofantrine and quinidine. Torsades de pointes has been reported in patients who received concomitant quinine and astemizole. Therefore, concurrent use of Quinine-ODAN with these medications, or drugs with similar properties, should be avoided [*see Drug Interactions*].
Concomitant administration of Quinine-ODAN with the antimalarial drugs, mefloquine or halofantrine, may result in electrocardiographic abnormalities, including QT prolongation, and increase the risk for torsades de pointes or other serious ventricular arrhythmias. Quinine-ODAN should also be avoided in patients with known prolongation of QT interval and in patients with clinical conditions known to prolong the QT interval, such as uncorrected hypokalemia, bradycardia, and certain cardiac conditions [*see Contraindications*].

Atrial Fibrillation and Flutter

Quinine-ODAN should be used with caution in patients with atrial fibrillation or atrial flutter. A paradoxical increase in ventricular response rate may occur with quinine, similar to that observed with quinidine. If digoxin is used to prevent a rapid ventricular response, serum digoxin levels should be closely monitored, because digoxin levels may be increased with use of quinine [*see Drug Interactions*].

Hematologic

Thrombocytopenia

Quinine-induced thrombocytopenia is an immune-mediated disorder. Severe cases of thrombocytopenia that are fatal or life threatening have been reported, including cases of HUS/TTP. Chronic renal impairment associated with the development of TTP has also been reported. Thrombocytopenia usually resolves within a week upon discontinuation of quinine. If quinine is not stopped, a patient is at risk for fatal hemorrhage. Upon re-exposure to quinine from any source, a patient with quinine-dependent antibodies could develop thrombocytopenia that is more rapid in onset and more severe than the original episode.

Hepatic/Biliary/Pancreatic

Hepatic

Close monitoring is recommended for patients with impaired liver function, as this may result in increased exposure to quinine.

Hypoglycemia

Quinine stimulates release of insulin from the pancreas, and patients, especially pregnant women, may experience clinically significant hypoglycemia.

Immune

Hypersensitivity

Serious hypersensitivity reactions reported with quinine sulfate include anaphylactic shock, anaphylactoid reactions, urticaria, serious skin rashes, including Stevens-Johnson

syndrome and toxic epidermal necrolysis, angioedema, facial edema, bronchospasm, and pruritus.
A number of other serious adverse reactions reported with quinine, including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), thrombocytopenia, immune thrombocytopenic purpura (ITP), blackwater fever, disseminated intravascular coagulation, leukopenia, neutropenia, granulomatous hepatitis, and acute interstitial nephritis may also be due to hypersensitivity reactions.

Quinine-ODAN should be discontinued if there are any signs or symptoms of hypersensitivity [*see Contraindications*].

Musculoskeletal
Quinine has neuromuscular blocking activity, and may exacerbate myasthenia gravis.

Neurologic
Concurrent use of Quinine-ODAN and mefloquine may increase the risk of seizures [*see Drug Interactions*].

Renal
Clearance of quinine is decreased in patients with severe chronic renal failure; the dosage and dosing frequency of quinine sulfate should be reduced in these patients. The effects of mild and moderate renal impairment on the safety and pharmacokinetics of quinine sulfate are not known.

Special Populations

Pregnant Women:
Published data on over 1,000 pregnancy exposures to quinine did not show an increase in teratogenic effects over the background rate in the general population; however the majority of these exposures were not in the first trimester. In developmental and reproductive toxicity studies, central nervous system (CNS) and ear abnormalities and increased fetal deaths occurred in some species when pregnant animals received quinine at doses about 1 to 4 times the human clinical dose. Quinine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
P. falciparum malaria carries a higher risk of morbidity and mortality in pregnant women than in the general population. Pregnant women with P. falciparum malaria have an increased incidence of fetal loss (including spontaneous abortion and stillbirth), preterm labor and delivery, intrauterine growth retardation, low birth weight, and maternal death. Therefore, treatment of malaria in pregnancy is important.
Hypoglycemia, due to increased pancreatic secretion of insulin, has been associated with quinine use, particularly in pregnant women.
No information is available on the effect of quinine on fertility in animals or humans.
Nursing Women:
Quinine is distributed into breast milk. Although quinine is generally considered compatible with breastfeeding, the risks and benefits to infant and mother should be assessed. Caution should be exercised when administered to a nursing woman.

Pediatrics: Quinine is considered acceptable for use in children at doses recommended for the treatment of malaria.
Geriatrics: Reported clinical experience has not identified differences in responses between the elderly and younger patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse events associated with quinine use are a cluster of symptoms called "cinchonism", which occurs to some degree in almost all patients taking quinine. Symptoms of mild cinchonism include headache, vasodilation and sweating, nausea, tinnitus, hearing impairment, vertigo or dizziness, blurred vision, and disturbance in color perception. More severe symptoms of cinchonism are vomiting, diarrhea, abdominal pain, deafness, blindness, and disturbances in cardiac rhythm or conduction. Most symptoms of cinchonism are reversible and resolve with discontinuation of quinine.

The following ADVERSE REACTIONS have been reported with quinine sulfate. Most of these reactions are thought to be uncommon, but the actual incidence is unknown:

Blood and lymphatic system disorders: agranulocytosis, hypoprothrombinemia, thrombocytopenia, disseminated intravascular coagulation, hemolytic anemia; hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura, petechiae, ecchymosis, hemorrhage, coagulopathy, blackwater fever, leukopenia, neutropenia, pancytopenia, aplastic anemia.
Cardiac disorders: chest pain, tachycardia, bradycardia, palpitations, syncope, atrioventricular block, atrial fibrillation, irregular rhythm, unifocal premature ventricular contractions, nodal escape beats, U waves, QT prolongation, ventricular fibrillation, ventricular tachycardia, torsades de pointes, and cardiac arrest.
Ear and labyrinth disorders: vertigo, tinnitus, hearing impairment, and deafness.
Eye disorders: visual disturbances, including blurred vision with scotomata, sudden loss of vision, photophobia, diplopia, night blindness, diminished visual fields, fixed pupillary dilatation, disturbed color vision, optic neuritis, blindness.
Gastrointestinal system disorders: nausea, vomiting, diarrhea, abdominal pain, gastric irritation, and esophagitis.
Hepatobiliary disorders: granulomatous hepatitis, hepatitis, jaundice, and abnormal liver function tests.
Immune system disorders: fever, chills, sweating, flushing, lupus-like syndrome, and hypersensitivity reactions.
Metabolism and nutrition disorders: hypoglycemia and anorexia.
Musculoskeletal system disorders: myalgias and muscle weakness.
Nervous system disorders: headache, diplopia, confusion, altered mental status, seizures, coma, disorientation, tremors, restlessness, ataxia, acute dystonic reaction, aphasia, and suicide.
Renal disorders: hemoglobinuria, renal failure, renal impairment, and acute interstitial nephritis.
Respiratory disorders: asthma, dyspnea, pulmonary edema.

Skin and subcutaneous tissue disorders: cutaneous rashes, including urticarial, papular, or scarlatinal rashes, pruritus, bullous dermatitis, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, fixed drug eruption, photosensitivity reactions, allergic contact dermatitis, acral necrosis, and cutaneous vasculitis.
Vascular disorders: vasodilatation, hypotension, postural hypotension.

DRUG INTERACTIONS

Overview
Quinine is a P-gp substrate and is primarily metabolized by CYP3A4. Other enzymes, including CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 may contribute to the metabolism of quinine. Results of in vivo drug interaction studies suggest that quinine has the potential to inhibit the metabolism of drugs that are substrates of CYP3A4 and CYP2D6. Quinine inhibits P-gp and has the potential to affect the transport of drugs that are P-gp substrates.

Drug-Drug Interactions

Effects of Drugs and Other Substances on Quinine Pharmacokinetics
Quinine is a P-gp substrate and is primarily metabolized by CYP3A4. Other enzymes, including CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 may contribute to the metabolism of quinine.
Hepatic Microsomal Enzyme Inhibitors: Inhibitors of CYP 3A4 may decrease the metabolism of quinine. Although the clinical significance of this interaction is unknown, drugs such as cyclosporine, antifungal agents (e.g. itraconazole, ketoconazole), macrolide antibiotics including erythromycin and clarithromycin, antidepressants (e.g. nefazodone), and HIV protease inhibitors (e.g. ritonavir) or other agents which inhibit CYP 3A4, should be avoided.
Hepatic Microsomal Enzyme Inducers: Inducers of CYP 3A4 may increase the metabolism of quinine and may decrease quinine plasma concentrations if used concurrently with Quinine-ODAN (eg. carbamazepine, phenobarbital, and phenytoin)
Antacids: Antacids containing aluminum and/or magnesium may delay or decrease absorption of quinine. Concomitant administration of these antacids with Quinine-ODAN should be avoided.
Urinary alkalizers (acetazolamide, sodium bicarbonate): Agents which increase urinary pH may inhibit the renal excretion of quinine and increase the risk of quinine toxicity.

Effects of Quinine on the Pharmacokinetics of Other Drugs
Results of in vivo drug interaction studies suggest that quinine has the potential to inhibit the metabolism of drugs that are substrates of CYP3A4 and CYP2D6. Quinine inhibits P-gp and has the potential to affect the transport of drugs that are P-gp substrates.
Astemizole (CYP3A4 substrate): Elevated plasma astemizole concentrations were reported in a subject who experienced torsades de pointes after receiving three doses of quinine sulfate for nocturnal leg cramps concomitantly with chronic astemizole

10 mg/day. The concurrent use of Quinine-ODAN with astemizole and other CYP3A4 substrates with QT prolongation potential (e.g., **cisapride, terfenadine, halofantrine, pimozide and quinidine)** should also be avoided [*see Warnings and Precautions*].
Atorvastatin (CYP3A4 substrate): Rhabdomyolysis with acute renal failure secondary to myoglobinuria was reported in a patient taking atorvastatin administered with a single dose of quinine. Quinine may increase plasma concentrations of atorvastatin, thereby increasing the risk of myopathy or rhabdomyolysis. Thus, clinicians considering combined therapy of Quinine-ODAN with atorvastatin or other HMG-CoA reductase inhibitors ("statins") that are CYP3A4 substrates (e.g., simvastatin, lovastatin) should carefully weigh the potential benefits and risks of each medication. If Quinine-ODAN is used concomitantly with any of these statins, lower starting and maintenance doses of the statin should be considered. Patients should also be monitored closely for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during initial therapy. If marked creatine phosphokinase (CPK) elevation occurs or myopathy (defined as muscle aches or muscle weakness in conjunction with CPK values >10 times the upper limit of normal) is diagnosed or suspected, atorvastatin or other statin should be discontinued.
Digoxin (P-gp substrate): Quinine increases plasma concentrations of digoxin. Thus, if Quinine-ODAN is administered to patients receiving digoxin, plasma digoxin concentrations should be closely monitored, and the digoxin dose adjusted as necessary [*see Warnings and Precautions*].
Mefloquine: The concomitant administration of mefloquine and Quinine-ODAN may produce electrocardiographic abnormalities (including QTc prolongation) and may increase the risk of seizures [*see Warnings and Precautions*].
Neuromuscular blocking agents (pancuronium, succinylcholine, tubocurarine): Quinine may potentiate the effects of neuromuscular blockers such as pancuronium, succinylcholine and tubocurarine resulting in respiratory difficulties. [*see Warnings and Precautions*].
Warfarin and oral anticoagulants: Cinchona alkaloids, including quinine, may have the potential to depress hepatic enzyme synthesis of vitamin K-dependent coagulation pathway proteins and may enhance the action of warfarin and other oral anticoagulants. Quinine may also interfere with the anticoagulant effect of heparin. Thus, in patients receiving these anticoagulants, the prothrombin time (PT), partial thromboplastin time (PTT), or international normalization ratio (INR) should be closely monitored as appropriate, during concurrent therapy with Quinine-ODAN.

Drug-Laboratory Interactions
Quinine may produce an elevated value for urinary 17-ketogenic steroids when the Zimmerman method is used.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Quinine sulfate 300 mg is approximately equivalent to quinine base 250 mg.

Patients should be instructed to:
- Take all of the medication as directed.

- Take no more of the medication than the amount prescribed.
- Take with food to minimize possible gastrointestinal irritation.

Completion of a 7-day oral quinine treatment regimen may be limited by drug intolerance, and shorter courses (3 days) of quinine combination therapy have been used. However, the published data from randomized, controlled clinical trials for shorter regimens of oral quinine in conjunction with tetracycline, doxycycline, or clindamycin for treatment of uncomplicated *P. falciparum* malaria are limited, and these shorter course combination regimens may not be as effective as the longer regimens.

Recommended Dose and Dosage Adjustment
Adults: (≥ 16 years of age): Quinine sulfate 600 mg (500 mg quinine base) every 8 hours, for 3 to 7 days.
Children: (<16 years): Quinine sulfate 9 mg/kg (7.5 mg quinine base/kg) to a maximum of 600 mg (500 mg quinine base) every 8 hours, for 3 to 7 days.

• Patients with severe chronic renal impairment: one loading dose of 600 mg quinine sulphate followed 12 hours later by 300 mg quinine sulfate every 12 hours for 7 days.

Missed Dose
If a dose is missed, patients should be instructed not to double the next dose. If more than 4 hours has elapsed since the missed dose, the patient should wait and take the next dose as previously scheduled.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Quinine overdose can be associated with serious complications, including visual impairment, hypoglycemia, cardiac arrhythmias, and death. Visual impairment can range from blurred vision and defective color perception, to visual field constriction and permanent blindness.

Cinchonism occurs in virtually all patients with quinine overdose. Symptoms range from headache, nausea, vomiting, abdominal pain, diarrhea, tinnitus, vertigo, hearing impairment, sweating, flushing, and blurred vision, to deafness, blindness, serious cardiac arrhythmias, hypotension, and circulatory collapse. Central nervous system toxicity (drowsiness, disturbances of consciousness, ataxia, convulsions, respiratory depression and coma) has also been reported with quinine overdose, as well as pulmonary edema and adult respiratory distress syndrome.

Most toxic reactions are dose-related; however, some reactions may be idiosyncratic because of the variable sensitivity of patients to the toxic effects of quinine. A lethal dose of quinine has not been clearly defined, but fatalities have been reported after the ingestion of 2 to 8 grams in adults.

Quinine, like quinidine, has Class I antiarrhythmic properties. The cardiotoxicity of quinine is due to its negative inotropic action, and to its effect on cardiac conduction, resulting in decreased rates of depolarization and conduction, and increased action potential and effective refractory period. ECG changes observed with quinine overdose include sinus tachycardia, PR prolongation, T wave inversion, bundle branch block, an increased QT interval, and a widening of the QRS complex. Quinine's alpha-blocking properties may result in hypotension and further exacerbate myocardial depression by decreasing coronary perfusion. Quinine overdose has been also associated with hypotension, cardiogenic shock, and circulatory collapse, ventricular arrhythmias, including ventricular tachycardia, ventricular fibrillation, idioventricular rhythm, and torsades de pointes, as well as bradycardia, and atrioventricular block.

Quinine is rapidly absorbed, and attempts to remove residual quinine sulfate from the stomach by gastric lavage may not be effective. Multiple-dose activated charcoal has been shown to decrease plasma quinine concentrations. Forced acid diuresis, hemodialysis, charcoal column hemoperfusion, and plasma exchange were not found to be effective in significantly increasing quinine elimination.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Quinine is an antimalarial agent. Quinine inhibits nucleic acid synthesis, protein synthesis, and glycolysis in *Plasmodium falciparum* and can bind with hemazoin in parasitized erythrocytes. However, the precise mechanism of the antimalarial activity of quinine sulfate is not completely understood.

Quinine sulfate acts primarily on the blood schizont form of *P. falciparum*. It is not gametocidal and has little effect on the sporozoite or pre-erythrocytic forms.

Strains of *P. falciparum* with decreased susceptibility to quinine can be selected *in vivo*. *P. falciparum* malaria that is clinically resistant to quinine has been reported in some areas of South America, Southeast Asia, and Bangladesh.

Pharmacokinetics

Following oral administration, quinine is rapidly and almost completely absorbed from the gastrointestinal tract. It is widely distributed to body tissues and approximately 70% protein bound. Quinine readily crosses the placenta and is excreted into breast milk. Concentrations in cerebrospinal fluid are 2 to 7% of plasma levels. Quinine is metabolized in the liver by the cytochrome P450 isoenzyme CYP3A4 and excreted mainly in the urine. Anywhere from <5 to 20% of the drug is excreted unchanged in the urine. Renal excretion of the drug is enhanced at low urinary pH. The elimination half-life of quinine in healthy individuals ranges from 7 to 12 hours. Plasma concentrations of the drug may be higher and the half-life longer in patients with malaria due to impaired hepatic metabolism of the drug.

STORAGE AND STABILITY

Store at controlled room temperature 15ºC to 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Supplied:

Quinine-ODAN 200 mg Capsules: Each clear gelatine capsule monogrammed ODAN 200 contains Quinine Sulfate USP 200 mg. Supplied in bottles of 100 and 500 capsules.

Quinine-ODAN 300 mg Capsules: Each clear gelatine capsule monogrammed ODAN 300 contains Quinine Sulfate USP 300 mg. Supplied in bottles of 100 and 500 capsules.

Quinine-ODAN 300 mg Tablets: Each white round scored tablet monogrammed ODAN 300 contains Quinine Sulfate USP 300 mg. Supplied in bottles of 100 tablets.

Quinine-ODAN 200 and 300 mg Capsules contains the following non-medicinal ingredients: Corn Starch, Croscarmellose Sodium, Microcrystalline Cellulose, Sodium Lauryl sulphate, Stearic Acid, Talc and Gelatine.

Quinine-ODAN 300 mg Tablets contains the following non-medicinal ingredients: Colloidal Silicon Dioxide, Corn Starch, Croscarmellose Sodium, Microcrystalline Cellulose, Sodium Lauryl sulphate, Stearic Acid, Talc and Gelatine.

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