QUINIDINE GLUCONATE EXTENDED-RELEASE TABLETS USP 8/09

DESCRIPTION
Quinidine is antimalarial schizonticide and an antiarrhythmic agent with Class Ia activity; it is
the d-isomer of quinine, and its molecular weight is 323.45. Quinidine gluconate is the glucose
salt of quinidine; its chemical name is cinchon-9-α-D-glucoside (5S,5’-α-D-glucuronide); its
structural formula is:

Its empirical formula is C₂₀H₂₄N₂O₂ • C₆H₁₂O₇, and its molecular weight is 528.56, of which
62.3% is quinidine; its salt of quinidine; its chemical name is cinchonan-9-ol, 6’-methoxy-, (9S)-,
mono-D-gluconate; its molecular formula is C₂₀H₂₄N₂O₆ • C₆H₁₂O₇.

Each quinidine gluconate extended-release tablet contains 324 mg of quinidine gluconate (202 mg of
quinidine) in a matrix so designed as to provide better guidance than serum drug levels (see
CLINICAL PHARMACOLOGY: Clinical Effects). In a meta-analysis, quinidine was associated with a statistically significant threefold relative risk
of thromboembolism and/or stroke, but these benefits have never been demonstrated in clinical trials. Some
patients have been re-exposed to quinidine after receiving quinidine-dependent antibodies. These
patients may lose these antibodies over time, but those with myasthenia gravis, might be
adversely affected by an anticholinergic agent.

WARNINGS
In many trials of antiarrhythmic therapy for non-life-threatening arrhythmias, active
antiarrhythmic therapy has resulted in increased mortality; the risk of active therapy is
probably greatest in patients with structural heart disease.

In the case of quinidine used to prevent or defer recurrence of atrial fibrillation/flutter, the
best available data come from a meta-analysis described under CLINICAL
PHARMACOLOGY: Clinical Effects above. In the patients studied in the trials there
analyzed, the mortality associated with the use of quinidine was more than three times
greater than that associated with the use of any of a variety of alternative antiarrhythmics.

Quinidine-induced thrombocytopenia is an immune-mediated disorder characterized by a
drug-dependent antibody that is self-reactive, but when soluble drug is present at pharmacologic
concentrations, binds tightly to specific platelet epitopes. It occurs in up to 3% of
patients given quinidine. 1 The most frequent presentation is a fall in circulating platelet counts
with a subsequent thrombocytopenia of 20 to 80% of normal. 2 When quinidine is
administered to patients with atrial flutter/fibrillation, the desired pharmacologic
endpoint is the control of both the underlying rhythm as well as the ventricular rate
with a consequent reduction in the risk of thromboembolism and/or stroke. The
resulting ventricular rate may be further reduced to less than 100 beats per
minute. 3 This rate reduction may be achieved by the use of digitalis
preparations or by various in vitro techniques. 4,5 Quinidine has at least the same antiarrhythmic activity of the parent
compound, so it may be used for a substantial portion of the effect of quinidine
 gluconate in chronic use.

In patients with atrial fibrillation/flutter, quinidine levels are decreased by coadministration of
aluminum-hydroxide antacids. The rate of absorption of quinidine following
administration of quinidine may be decreased by coadministration of
acetaminophen. The rate of absorption of quinidine may be decreased by
absorption of quinidine from quinidine gluconate tablets is significantly
improved by the ingestion of grapefruit juice.

PRECAUTIONS
Intraocular pressure in patients with glaucoma should be monitored when quinidine
is administered.

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The most serious quinidine-associated adverse reactions are described above under WARNINGS.

**WARNINGS**

- **slow-release quinidine bisulfate tablets, 600 mg (approximately 400 mg of quinidine base) twice daily.**

The adverse reactions most frequently reported are gastrointestinal, including diarrhea, nausea, vomiting, and abdominal pain. These effects are typically transient and may be reversed by adjusting the dose or by stopping therapy. Other reactions, although less frequent, may include headache, dizziness, tinnitus, dysuria, dyspepsia, vomiting, diarrhea, dermatologic reactions, alopecia, and pruritus.

- **Administration of quinidine should (if possible) be avoided in lactating women.** Quinidine is present in human milk at levels slightly lower than those in maternal serum; a human milk level of 31 mg/liter (0.11 mg/ml) was found in one study. The low total serum levels at least an order of magnitude lower than those of the mother. On the other hand, the pharmacokinetics and pharmacodynamics of quinidine in human infants have not been adequately studied.

- **Quinidine's anticholinergic, vasodilating, and antiparkinsonian effects may contribute to the increased incidence of syncope. Acute psychotic reactions have been reported to follow the first dose of quinidine, simply the results of hypotension and consequent cerebral hypoperfusion.** There are many reports of syncope, including cases of syncope without hypotension. Other signs and symptoms of overdose may include vomiting, diarrhea, tinnitus, dysuria, dyspepsia, vomiting, diarrhea, dermatologic reactions, alopecia, and pruritus.

- **Quinidine therapy has been associated with the development of immune thrombocytopenia.** Perhaps by competing for pathways of renal clearance, coadministration of quinidine causes an increase in the amount of an unknown metabolite that is converted to the IgG antibody. The antibody is then directed against the metabolite, resulting in a reduction of platelets. This phenomenon has been observed in patients taking quinidine and other drugs that are metabolized by the N-acetyltransferase pathway. See also DRUG INTERACTIONS.

- **Hypotension** has been reported in patients receiving quinidine. The dose of quinidine should be reduced or administration should be withheld in patients with hypotension. Other signs and symptoms of overdose may include vomiting, diarrhea, tinnitus, dysuria, dyspepsia, vomiting, diarrhea, dermatologic reactions, alopecia, and pruritus.

- **Arrhythmias** have been reported in patients receiving quinidine. The dose of quinidine should be reduced or administration should be withheld in patients with arrhythmias. Other signs and symptoms of overdose may include vomiting, diarrhea, tinnitus, dysuria, dyspepsia, vomiting, diarrhea, dermatologic reactions, alopecia, and pruritus.

- **Suppression of life-threatening ventricular arrhythmias.** Dosing regimens for the use of quinidine gluconate in suppressing life-threatening ventricular arrhythmias have not been adequately studied. Described regimens of various oral formulations of quinidine have been well described. Death has been described after a 5-g ingestion by a toddler, while an adolescent was reported to survive after consuming a 10-g dose. Other serious and fatal effects of quinidine overdosage include respiratory depression, ventricular fibrillation, hypotension, fever, hypothermia, hypoglycemia, gastrointestinal bleeding, extrapyramidal reactions (including posterior muscle necrosis), pulmonary edema, cardiac arrest, delayed myocardial necrosis, and death.

**DOSE AND ADMINISTRATION**

The dose of quinidine gluconate extended-release tablets may be titrated by breaking a tablet in half. If tablets are crushed or chewed, their extended-release properties may be altered.

The dosage of quinidine varies considerably depending on the patient’s clinical state.

**Conversion of atrial fibrillation/flutter to sinus rhythm**

- **In patients with known structural heart disease having atrial fibrillation/flutter who may have other risk factors for toxicity, initiation of quinidine therapy should include an increase in the dose at a slower rate (e.g., 25 to 50 mg every 2 or 3 days).** In one report, the increased incidence of syncope and other adverse reactions was accompanied by a decrease in plasma quinidine concentration. The dose should be increased only as required to achieve the desired clinical benefits in poor metabolizers.

- **When quinidine and verapamil are coadministered,** the pharmacokinetics and pharmacodynamics of quinidine in human infants have not been adequately studied.

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**OVERDOSE**

- **Acute thrombocytopenic purpura in relation to the use of drugs.**

**INFORMATION FOR PATIENTS**

- **that such data as are available suggest that treatment with quinidine gluconate is likely to**

**ADVERSE REACTIONS**

**IN PATIENTS WITH ATRIAL FIBRILLATION**

<table>
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<td>fever</td>
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Vomiting and diarrhea can occur as idiosyncratic reactions to therapeutic levels of quinidine, but they may also be the first signs of cinchonism, a syndrome that may also include tinnitus, reversible high frequency hearing loss, vertigo, visual field loss, photosensitivity, and abnormalities of pigmentation.

**ADVERSE REACTIONS EXPERIENCED MORE THAN ONCE**

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- **Diabetes**

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