

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DEXTROMETHORPHAN HYDROBROMIDE AND QUINIDINE SULFATE CAPSULES safely and effectively. See full prescribing information for DEXTROMETHORPHAN HYDROBROMIDE AND QUINIDINE SULFATE CAPSULES.
DEXTROMETHORPHAN HYDROBROMIDE AND QUINIDINE SULFATE capsules, for oral use
Initial U.S. Approval: 2010

INDICATIONS AND USAGE
Dextromethorphan hydrobromide and quinidine sulfate capsules are a combination product containing dextromethorphan hydrobromide (an uncompetitive NMDA receptor antagonist and sigma-1 agonist) and quinidine sulfate (a CYP450 2D6 inhibitor) indicated for the treatment of pseudobulbar affect (PBA). (1)

DOSE AND ADMINISTRATION
• Starting dose: one capsule daily by mouth for 7 days. (2.1)
• Maintenance dose: After 7 days, 1 capsule every 12 hours. (2.1)

DOSE FORMS AND STRENGTHS
Capsules: Dextromethorphan hydrobromide 20 mg/quinidine sulfate 10 mg. (3)

CONTRAINDICATIONS
• Concomitant use with quinidine, quinine, or mefloquine. (4.1)
• Patients with a history of quinidine, quinine or mefloquine-induced thrombocytopenia, hepatitis, or other hypersensitivity reactions. (4.2)
• Patients with known hypersensitivity to dextromethorphan. (4.2)
• Use with an MAOI or within 14 days of stopping an MAOI. Allow 14 days after stopping dextromethorphan hydrobromide and quinidine sulfate before starting an MAOI. (4.3)
• Prolonged QT interval, congenital long QT syndrome, history suggestive of torsades de pointes, or heart failure. (4.4)
• Complete atrioventricular (AV) block without implanted pacemaker, or patients at high risk of complete AV block. (4.4)
• Concomitant use with drugs that both prolong QT interval and are metabolized by CYP2D6 (e.g., thioridazine or pimozide). (4.4)

WARNINGS AND PRECAUTIONS
• Thrombocytopenia or other hypersensitivity reactions: Discontinue if occurs. (5.1)
• Hepatitis: Discontinue if occurs. (5.2)

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- QT Prolongation: Monitor ECG if concomitant use of drugs that prolong QT interval cannot be avoided or if concomitant CYP3A4 inhibitors used. (5.3)
- Left ventricular hypertrophy (LVH) or left ventricular dysfunction (LVD): Monitor ECG in patients with LVH or LVD. (5.3)
- CYP2D6 substrate: Dextromethorphan hydrobromide and quinidine sulfate inhibits CYP2D6: Accumulation of parent drug and/or failure of metabolite formation may decrease safety and/or efficacy of concomitant CYP2D6 metabolized drugs. Adjust dose of CYP2D6 substrate or use alternative treatment when clinically indicated. (5.4, 12.4)
- Dizziness: Take precautions to reduce falls. (5.5)
- Serotonin syndrome: Use of dextromethorphan hydrobromide and quinidine sulfate with selective serotonin reuptake inhibitor (SSRIs) or tricyclic antidepressants increases the risk. Discontinue if occurs. (5.6, 7.4)
- Anticholinergic effects of quinidine: Monitor for worsening in myasthenia gravis and other sensitive conditions. (5.7)

ADVERSE REACTIONS
The most common adverse reactions (incidence of $\geq 3\%$ and two-fold greater than placebo) in patients taking dextromethorphan hydrobromide and quinidine sulfate are diarrhea, dizziness, cough, vomiting, asthenia, peripheral edema, urinary tract infection, influenza, increased gamma-glutamyltransferase, and flatulence. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
• Desipramine: Exposure increases 8-fold. Reduce desipramine dose and adjust based on clinical response. (7.5, 12.4)
• Paroxetine: Exposure increases 2-fold. Reduce paroxetine dose and adjust based on clinical response. (7.5, 12.4)
• Digoxin: Increased digoxin substrate plasma concentration may occur. (7.6)

USE IN SPECIFIC POPULATIONS

• Pregnancy: Based on animal data, may cause fetal harm. (8.1)
See 17 for PATIENT COUNSELING INFORMATION

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Dextromethorphan hydrobromide and quinidine sulfate capsules are indicated for the treatment of pseudobulbar affect (PBA).

PBA occurs secondary to a variety of otherwise unrelated neurologic conditions, and is characterized by involuntary, sudden, and frequent episodes of laughing and/or crying. PBA episodes typically occur out of proportion or incongruent to the underlying emotional state. PBA is a specific condition, distinct from other types of emotional lability that may occur in patients with neurological disease or injury.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended starting dose of dextromethorphan hydrobromide and quinidine sulfate capsules are one capsule daily by mouth for the initial seven days of therapy. On the eighth day of therapy and thereafter, the daily dose should be a total of two capsules a day, given as one capsule every 12 hours. The need for continued treatment should be reassessed periodically, as spontaneous improvement of PBA occurs in some patients.

3 DOSAGE FORMS AND STRENGTHS

Dextromethorphan hydrobromide and quinidine sulfate capsules contain 20 mg dextromethorphan hydrobromide and 10 mg quinidine sulfate in a white to off-white colored opaque hard gelatin capsule imprinted with "H" on cap with black ink and "D22" on body with black ink filled with white to off-white powder.

4 CONTRAINDICATIONS

4.1 Quinidine and Related Drugs

Dextromethorphan hydrobromide and quinidine sulfate capsules contain quinidine and should not be used concomitantly with other drugs containing quinidine, quinine, or mefloquine.

4.2 Hypersensitivity

Dextromethorphan hydrobromide and quinidine sulfate capsules are contraindicated in patients with a history of dextromethorphan hydrobromide and quinidine sulfate, quinine, mefloquine or quinidine-induced thrombocytopenia, hepatitis, bone marrow depression or lupus-like syndrome. Dextromethorphan hydrobromide and quinidine sulfate capsules are also contraindicated in patients with a known hypersensitivity to dextromethorphan (e.g. rash, hives) [see Warnings and Precautions (5.1)].

4.3 MAOIs

Dextromethorphan hydrobromide and quinidine sulfate capsules are contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or in patients who have taken MAOIs within the preceding 14 days, due to the risk of serious and possibly fatal drug interactions, including serotonin syndrome. Allow at least 14 days after stopping dextromethorphan hydrobromide and quinidine sulfate capsules before starting an MAOI [see Drug Interactions (7.1)].

4.4 Cardiovascular

Dextromethorphan hydrobromide and quinidine sulfate capsules are contraindicated in patients with a prolonged QT interval, congenital long QT syndrome or a history suggestive of torsades de pointes, and in patients with heart failure [see Warnings and Precautions (5.3)].

Dextromethorphan hydrobromide and quinidine sulfate capsules are contraindicated in patients receiving drugs that both prolong QT interval and are metabolized by CYP2D6 (e.g., thioridazine and pimozide), as effects on QT interval may be increased [see Drug Interactions (7.2)].

Dextromethorphan hydrobromide and quinidine sulfate capsules are contraindicated in patients with complete atrioventricular (AV) block without implanted pacemakers, or in patients who are at high risk of complete AV block.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombocytopenia and Other Hypersensitivity Reactions

Quinidine can cause immune-mediated thrombocytopenia that can be severe or fatal. Non-specific symptoms, such as lightheadedness, chills, fever, nausea, and vomiting, can precede or occur with thrombocytopenia. Dextromethorphan hydrobromide and quinidine sulfate should be discontinued immediately if thrombocytopenia occurs, unless the thrombocytopenia is clearly not drug-related, as continued use increases the risk for fatal hemorrhage. Likewise, dextromethorphan hydrobromide and quinidine sulfate should not be restarted in sensitized patients, because more rapid and more severe thrombocytopenia than the original episode can occur. Dextromethorphan hydrobromide and quinidine sulfate should not be used if immune-mediated thrombocytopenia from structurally related drugs, including quinine and mefloquine is suspected, as cross-sensitivity can occur. Quinidine-associated thrombocytopenia usually, but not always, resolves within a few days of discontinuation of the sensitizing drug.

Quinidine has also been associated with a lupus-like syndrome involving polyarthritides, sometimes with a positive antinuclear antibody test. Other associations include rash, bronchospasm, lymphadenopathy, hemolytic anemia, vasculitis, uveitis, angioedema, agranulocytosis, the sicca syndrome, myalgia, elevation in serum levels of skeletal-muscle enzymes, and pneumonitis.

5.2 Hepatotoxicity

Hepatitis, including granulomatous hepatitis, has been reported in patients receiving quinidine, generally during the first few weeks of therapy. Fever may be a presenting symptom, and thrombocytopenia or other signs of hypersensitivity may also occur. Most cases remit when quinidine is withdrawn.

5.3 Cardiac Effects

Dextromethorphan hydrobromide and quinidine sulfate causes dose-dependent QTc prolongation [see Clinical Pharmacology (12.2)]. QT prolongation can cause torsades de pointes-type ventricular tachycardia, with the risk increasing as the degree of prolongation increases. When initiating dextromethorphan hydrobromide and quinidine sulfate in patients at risk of QT prolongation and torsades de pointes, electrocardiographic (ECG) evaluation of QT interval should be conducted at baseline and 3 to 4 hours after the first dose. This includes patients concomitantly taking/initiating drugs that prolong the QT interval or that are strong or moderate CYP3A4 inhibitors, and patients with left ventricular hypertrophy (LVH) or left ventricular dysfunction (LVD). LVH and LVD are more likely to be present in patients with chronic hypertension, known coronary artery disease, or history of stroke. LVH and LVD can be diagnosed utilizing echocardiography or another suitable cardiac imaging modality.

Strong and moderate CYP3A4 inhibitors include, but are not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil.

Reevaluate ECG if risk factors for arrhythmia change during the course of treatment with dextromethorphan hydrobromide and quinidine sulfate. Risk factors include concomitant use of drugs associated with QT prolongation, electrolyte abnormality (hypokalemia, hypomagnesemia), bradycardia, and family history of QT abnormality. Hypokalemia and hypomagnesemia should be corrected prior to initiation of therapy with dextromethorphan hydrobromide and quinidine sulfate, and should be monitored during treatment.

If patients taking dextromethorphan hydrobromide and quinidine sulfate experience symptoms that could indicate the occurrence of cardiac arrhythmias, e.g., syncope or palpitations, dextromethorphan hydrobromide and quinidine sulfate should be discontinued and the patient further evaluated.

5.4 Concomitant use of CYP2D6 Substrates

The quinidine in dextromethorphan hydrobromide and quinidine sulfate inhibits CYP2D6 in patients in whom CYP2D6 is not otherwise genetically absent or its activity otherwise pharmacologically inhibited [see Warnings and Precautions (5.8) and Clinical Pharmacology (12.3), (12.5)]. Because of this effect on CYP2D6, accumulation of parent drug and/or failure of active metabolite formation may decrease the safety and/or the efficacy of drugs used concomitantly with dextromethorphan hydrobromide and quinidine sulfate that are metabolized by CYP2D6 [see Drug Interactions (7.5)].

5.5 Dizziness

Dextromethorphan hydrobromide and quinidine sulfate may cause dizziness [see Adverse Reactions (6.1)]. Precautions to reduce the risk of falls should be taken, particularly for patients with motor impairment affecting gait or a history of falls. In a controlled trial of dextromethorphan hydrobromide and quinidine sulfate, 10% of patients on dextromethorphan hydrobromide and quinidine sulfate and 5% on placebo experienced dizziness.

5.6 Serotonin Syndrome

When used with SSRIs (such as fluoxetine) or tricyclic antidepressants (such as clomipramine and imipramine), dextromethorphan hydrobromide and quinidine sulfate may cause "serotonin syndrome", with changes including altered mental status, hypertension, restlessness, myoclonus, hyperthermia, hyperreflexia, diaphoresis, shivering, and tremor [see Drug Interactions (7.4), Overdosage (10)].

5.7 Anticholinergic Effects of Quinidine

Monitor for worsening clinical condition in myasthenia gravis and other conditions that may be adversely affected by anticholinergic effects.

5.8 CYP2D6 Poor Metabolizers

The quinidine component of dextromethorphan hydrobromide and quinidine sulfate is intended to inhibit CYP2D6 so that higher exposure to dextromethorphan can be achieved compared to when dextromethorphan is given alone [see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3), (12.5)]. Approximately 7% to 10% of Caucasians and 3 to 8% of African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PMs). The quinidine component of dextromethorphan hydrobromide and quinidine sulfate is not expected to contribute to the effectiveness of dextromethorphan hydrobromide and quinidine sulfate in PMs, but adverse events of the quinidine are still possible. In those patients who may be at risk of significant toxicity due to quinidine, genotyping to determine if they are PMs should be considered prior to making the decision to treat with dextromethorphan hydrobromide and quinidine sulfate.

6 ADVERSE REACTIONS

A total of 946 patients participated in four Phase 3 controlled and uncontrolled PBA studies and received at least one dose of the combination product of dextromethorphan/quinidine in various strengths at the recommended or higher than the recommended dose. Of those patients, 393 patients were exposed for at least 180 days and 294 patients were exposed for at least one year. Median exposure was 168 days.

Controlled trials enrolled only patients with either ALS or MS. Uncontrolled studies enrolled 136 patients with PBA secondary to a wide variety of underlying neurological conditions including stroke (45 patients) and traumatic brain injury (23 patients). Consequently, patients with other underlying neurologic diseases may experience other adverse reactions not described below.

6.1 Clinical Trials Experience

A 12-week, placebo-controlled study evaluated dextromethorphan hydrobromide and quinidine sulfate (dextromethorphan 20 mg/quinidine 10 mg) (N=107) and a 30 mg dextromethorphan/10 mg quinidine combination (N=110) compared to placebo (N=108). Approximately 60% of patients had ALS and 40% had MS. Patients were 25 to 80 years of age, with a mean age of approximately 51 years. Three (3) ALS patients in each drug treatment arm and 1 ALS patient in the placebo arm died during the 12-week placebo-control period. All deaths were consistent with the natural progression of ALS.

Adverse Reactions Leading to Discontinuation

The most commonly reported adverse reactions (incidence $\geq 2\%$ and greater than placebo) that led to discontinuation with the 20 mg dextromethorphan/10 mg quinidine twice daily dose were muscle spasticity (3%), respiratory failure (1%), abdominal pain (2%), asthenia (2%), dizziness (2%), fall (1%), and muscle spasms (2%).

Most Common Adverse Reactions

Adverse drug reactions that occurred in $\geq 3\%$ of patients receiving the 20 mg dextromethorphan/10 mg quinidine twice daily dose, and at an incidence of ≥ 2 times placebo in short-term clinical trials in ALS and MS are provided in Table 1. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Table 1: Adverse Drug Reactions with an Incidence of $\geq 3\%$ of Patients and $> 2\times$ Placebo in Dextromethorphan Hydrobromide and Quinidine Sulfate-treated Patients by System-Organ Class and Preferred Term		
	Dextromethorphan Hydrobromide and Quinidine Sulfate N=107 %	Placebo N=108 %
Diarrhea	13	6
Dizziness	10	5
Cough	5	2
Vomiting	5	1
Asthenia	5	2
Peripheral edema	5	1
Urinary tract infection	4	1
Influenza	4	1
Increased gamma- glutamyltransferase	4	1
Flatulence	3	0

Dimensions	280 x 600 mm (Book Fold: 40 x 40 mm)
Customer/Country	Hetero Labs Limited / Camber
Spec	Bible Paper 40 GSM
Pantone Colours	Black
Version No.	00

Note: Pharma code position will be change as per folding machine feasibility at vendor.



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10.1 Treatment of Overdose

While serum quinidine levels can be measured, electrocardiographic monitoring of the QTc interval is a better predictor of quinidine-induced arrhythmia. Treatment of hemodynamically unstable polymorphic ventricular tachycardia (including torsades de pointes) is either immediate cardioversion or, if a cardiac pacemaker is in place or immediately available, immediate overdrive pacing. After pacing or cardioversion, further management must be guided by the length of the QTc interval. Factors contributing to QTc prolongation (especially hypokalemia and hypomagnesemia) should be sought out and (if possible) aggressively corrected. Prevention of recurrent torsades de pointes may require sustained overdrive pacing or the cautious administration of isoproterenol (30 to 150 ng/kg/min).

Because of the theoretical possibility of QT-prolonging effects that might be additive to those of quinidine, other antiarrhythmics with Class I (procainamide) or Class III activities should (if possible) be avoided.

If the post-cardioversion QTc interval is prolonged, then the pre-cardioversion polymorphic ventricular tachyarrhythmia was (by definition) torsades de pointes. In this case, class I antiarrhythmics like lidocaine are unlikely to be of value, and other Class I and Class III antiarrhythmics are likely to exacerbate the situation.

Quinidine-induced hypotension that is not due to an arrhythmia is likely to be a consequence of quinidine-related -blockade and vasorelaxation. Treatment of hypotension should be directed at symptomatic and supportive measures. Repletion of central volume (Trendelenburg positioning, saline infusion) may be sufficient therapy; other interventions reported to have been beneficial in this setting are those that increase peripheral vascular resistance, including -agonist catecholamines (norepinephrine).

Quinidine

Adequate studies of orally administered activated charcoal in human overdoses of quinidine have not been reported, but there are animal data showing significant enhancement of systemic elimination following this intervention, and there is at least one human case report in which the elimination half-life of quinidine in the serum was apparently shortened by repeated gastric lavage. Activated charcoal should be avoided if an ileus is present; the conventional dose is 1 gram/kg, administered every 2 to 6 hours as a slurry with 8 mL/kg of tap water. Although renal elimination of quinidine might theoretically be accelerated by maneuvers to acidify the urine, such maneuvers are potentially hazardous and of no demonstrated benefit. Quinidine is not usefully removed from the circulation by dialysis. Following quinidine overdose, drugs that delay elimination of quinidine (cimetidine, carbonic anhydrase inhibitors, thiazide diuretics) should be withdrawn unless absolutely required.

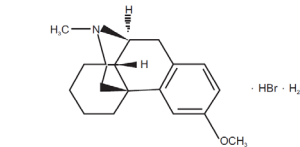
Dextromethorphan

Treatment of dextromethorphan overdose should be directed at symptomatic and supportive measures.

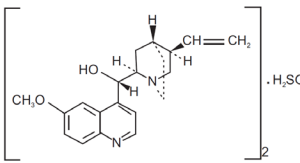
11 DESCRIPTION

Dextromethorphan hydrobromide and quinidine sulfate capsules are an oral formulation of dextromethorphan hydrobromide USP and quinidine sulfate USP in a fixed dose combination.

Dextromethorphan hydrobromide is the pharmacologically active ingredient of dextromethorphan hydrobromide and quinidine sulfate capsules that acts on the central nervous system (CNS). The chemical name of dextromethorphan hydrobromide is morphinan, 3-methoxy-17-methyl-, (8*a*, 13*a*, 14*a*), hydrobromide monohydrate. Dextromethorphan hydrobromide has the molecular formula C₁₈H₂₅NO4•HBr•H₂O with a molecular weight of 370.33. The structural formula is:



Quinidine sulfate is a specific inhibitor of CYP2D6-dependent oxidative metabolism used in dextromethorphan hydrobromide and quinidine sulfate capsules to increase the systemic bioavailability of dextromethorphan. The chemical name of quinidine sulfate is cinchon-9-*o*-1, 6'-methoxy-, (9*S*) sulfate (2:1), (salt), dihydrate. Quinidine sulfate dihydrate has the molecular formula of (C₂₀H₂₆N₂O₇)₂•H₂SO₄•2H₂O with a molecular weight of 782.96. The structural formula is:



The combination product, dextromethorphan hydrobromide and quinidine sulfate capsules, is a white to off-white powder. Dextromethorphan hydrobromide and quinidine sulfate capsules are available for oral use, which contains 20 mg dextromethorphan hydrobromide, USP and 10 mg quinidine sulfate, USP. The active ingredients are dextromethorphan hydrobromide, USP and quinidine sulfate, USP. Inactive ingredients in the capsule are colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose.

The capsule shell contains gelatin and titanium dioxide. The black imprinting ink contains ammonia solution, iron oxide black, potassium hydroxide, propylene glycol, and shellac.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dextromethorphan (DM) is a sigma-1 receptor agonist and an uncompetitive NMDA receptor antagonist. Quinidine increases plasma levels of dextromethorphan by competitively inhibiting cytochrome P450 2D6, which catalyzes a major biotransformation pathway for dextromethorphan. The mechanism by which dextromethorphan exerts therapeutic effects in patients with pseudobulbar affect is unknown.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of dextromethorphan 30 mg/quinidine 10 mg (for 7 doses) on QTc prolongation was evaluated in a randomized, double-blind (except for moxifloxacin), placebo- and positive-controlled (400 mg moxifloxacin) crossover through QT study in 50 fasted normal healthy men and women with CYP2D6 extensive metabolizer (EM) genotype. Mean changes in QTcF were 6.8 ms for dextromethorphan 30 mg/quinidine 10 mg and 9.1 ms for the reference positive control (moxifloxacin). The maximum mean (95% upper confidence bound) difference from placebo after baseline correction was 10.2 (12.6) ms. This test dose is adequate to represent the steady state exposure in patients with CYP2D6 extensive metabolizer phenotype.

The effects of supratherapeutic doses of dextromethorphan/quinidine (30 mg/30mg and 60mg/60mg, for 7 doses) on QTc prolongation was evaluated in a randomized, placebo-controlled, double-blind, crossover design with an additional open-label positive control (400 mg moxifloxacin) arm in 36 healthy volunteers. The maximum mean (95% upper confidence bound) differences from placebo after baseline-correction were 10.2 (14.6) and 18.4 (22.7) ms following dextromethorphan/quinidine doses of 30 mg/30 mg and 60/60 mg, respectively. The supratherapeutic doses are adequate to represent exposure increases due to drug-drug interactions and organ dysfunctions.

12.3 Pharmacokinetics

Dextromethorphan hydrobromide and quinidine sulfate contains dextromethorphan and quinidine, both of which are metabolized primarily by liver enzymes. Quinidine's primary plasma concentrations (C_{max}) of dextromethorphan hydrobromide and quinidine sulfate is to competitively inhibit the metabolism of dextromethorphan catalyzed by CYP2D6 in order to increase and prolong plasma concentrations of dextromethorphan [see Warnings and Precautions (5.4), (5.8), and Clinical Pharmacology (12.5)]. Studies were conducted with the individual components of dextromethorphan hydrobromide and quinidine sulfate in healthy subjects to determine single-dose and multiple-dose kinetics of orally administered dextromethorphan in combination with quinidine. The increase in dextromethorphan levels appeared approximately dose proportional when the dextromethorphan dose was increased from 20 mg to 30 mg in the presence of 10 mg of quinidine.

Absorption

Following single and repeated combination doses of dextromethorphan 30 mg/quinidine 10 mg, dextromethorphan/quinidine -treated subjects had an approximately 20-fold increase in dextromethorphan exposure compared to dextromethorphan given without quinidine.

Following repeated doses of dextromethorphan 30 mg/quinidine 10 mg and dextromethorphan 20 mg/ quinidine 10 mg (dextromethorphan hydrobromide and quinidine sulfate), the plasma concentrations (C_{max}) of dextromethorphan are reached approximately 3 to 4 hours after dosing and maximal plasma concentrations of quinidine are reached approximately 1 to 2 hours after dosing.

In extensive metabolizers, mean C_{max} and AUC₀₋₁₂ values of dextromethorphan and dextrophan increased as doses of dextromethorphan increased from 20 to 30 mg, mean C_{max} and AUC₀₋₁₂ values of quinidine appeared similar.

The mean plasma C_{max} of quinidine following twice daily co-administration of dextromethorphan 30 mg/quinidine 10 mg in patients with PBA was within 1 to 3% of the concentrations required for antiarrhythmic efficacy (2 to 5 mcg/mL).

Dextromethorphan hydrobromide and quinidine sulfate may be taken without regard to meals as food does not affect the exposure of dextromethorphan and quinidine significantly.

Distribution

After dextromethorphan hydrobromide and quinidine sulfate administration, protein binding remains essentially the same as that after administration of the individual components; dextromethorphan is approximately 60 to 70% protein bound and quinidine is approximately 80 to 89% protein bound.

Metabolism and Excretion

Dextromethorphan hydrobromide and quinidine sulfate is a combination product containing dextromethorphan and quinidine. Dextromethorphan is metabolized by CYP2D6 and quinidine is metabolized by CYP3A4. After dextromethorphan 30 mg/quinidine 30 mg administration in extensive metabolizers, the elimination half-life of dextromethorphan was approximately 13 hours and the elimination half-life of quinidine was approximately 7 hours.

There are several hydroxylated metabolites of quinidine. The major metabolite of quinidine is 3-hydroxyquinidine. The 3-hydroxymetabolite is considered to be at least half as pharmacologically active as quinidine with respect to cardiac effects such as QT prolongation.

When the urine pH is less than 7, about 20% of administered quinidine appears unchanged in the urine, but this fraction drops to as little as 5% when the urine is more alkaline. Renal clearance involves both glomerular filtration and active tubular secretion, moderated by (pH-dependent) tubular reabsorption.

Specific Populations

Geriatric Use

The pharmacokinetics of dextromethorphan/quinidine have not been investigated systematically in elderly subjects (aged > 65 years), although such subjects were included in the clinical program. A population pharmacokinetic analysis of 170 subjects (148 subjects < 65 years old and 22 subjects ≥ 65 years old) administered dextromethorphan 30 mg/quinidine 30 mg revealed similar pharmacokinetics in subjects < 65 years and those ≥ 65 years of age.

Pediatric Use

The pharmacokinetics of dextromethorphan hydrobromide and quinidine sulfate in pediatric patients have not been studied.

Gender

A population pharmacokinetic analysis based on data from 109 subjects (75 male; 34 female) showed no apparent gender differences in the pharmacokinetics of dextromethorphan hydrobromide and quinidine sulfate.

Race

A population pharmacokinetic analysis of race with 109 subjects (20 Caucasian; 71 Hispanic; 18 Black) revealed no apparent racial differences in the pharmacokinetics of dextromethorphan hydrobromide and quinidine sulfate.

Renal Impairment

In a study of a combination dose of dextromethorphan 30 mg/quinidine 30 mg TWICE DAILY in 12 subjects with mild (CLCR 50 to 80 mL/min) or moderate (CLCR 30 to 50 mL/min) renal impairment (6 each) compared to 9 healthy subjects (matched in gender, age, and weight range to impaired subjects), subjects showed little difference in quinidine or dextromethorphan pharmacokinetics compared to healthy subjects. Dose adjustment is, therefore, not required in mild or moderate renal impairment. Dextromethorphan hydrobromide and quinidine sulfate has not been studied in patients with severe renal impairment.

Hepatic Impairment

In a study of a combination dose of dextromethorphan 30 mg/quinidine 30 mg TWICE DAILY in 12 subjects with mild or moderate hepatic impairment (as indicated by the Child-Pugh method; 6 each) compared to 9 healthy subjects (matched in gender, age, and weight range to impaired subjects), subjects with moderate hepatic impairment showed similar dextromethorphan AUC and C_{max} and clearance compared to healthy subjects. Mild to moderate hepatic impairment had little effect on quinidine pharmacokinetics. Patients with moderate impairment showed an increased frequency of adverse events. Therefore, dosage adjustment is not required in patients with mild and moderate hepatic impairment, although additional monitoring for adverse reactions should be considered. Quinidine clearance is unaffected by hepatic cirrhosis, although there is an increased volume of distribution that leads to an increase in the elimination half-life. Neither dextromethorphan alone nor dextromethorphan hydrobromide and quinidine sulfate has been evaluated in patients with severe hepatic impairment.

12.4 Drug-Drug Interactions

The potential for dextromethorphan and quinidine to inhibit or induce cytochrome P450 in vitro were evaluated in human microsomes. Dextromethorphan did not inhibit (< 20% inhibition) any of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 in human liver microsomes at concentrations up to 5 microM. Quinidine did not inhibit (< 30% inhibition) CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4 in human microsomes at concentrations up to 5 microM. Quinidine inhibited CYP2D6 with a half maximal inhibitory concentration (IC₅₀) of less than 0.05 microM. Neither dextromethorphan nor quinidine induced CYP1A2, CYP2B6 or CYP3A4 in human hepatocytes at concentrations up to 4.8 microM.

Desipramine (CYP2D6 substrate)

Co-administration of dextromethorphan 30 mg/quinidine 30 mg with the tricyclic antidepressant desipramine, a CYP2D6 substrate, when desipramine was given at a dose of 25 mg once daily in 13 healthy volunteers resulted in an approximately 8-fold increase in steady state desipramine exposure (C_{max}) compared to desipramine given alone. Therefore, concomitant administration of dextromethorphan hydrobromide and quinidine sulfate and drugs undergoing CYP2D6 metabolism should be evaluated for appropriate dose adjustment or alternative medication if the concomitant medication depends primarily on CYP2D6 metabolism and has a narrow therapeutic index, or if it relies on CYP2D6 for conversion to an active species [see Warnings and Precautions (5.4)].

Paroxetine (CYP2D6 inhibitor and substrate)

Co-administration of the selective serotonin reuptake inhibitor paroxetine and a higher combination dose of dextromethorphan/quinidine (dextromethorphan 30 mg/quinidine 30 mg) was studied in 27 healthy volunteers. Group 1 (N = 14) received paroxetine 20 mg once daily for 12 days followed by the addition of dextromethorphan 30 mg/quinidine 30 mg twice daily for 8 days. Group 2 (N = 13) received dextromethorphan 30 mg/quinidine 30 mg twice daily for 8 days followed by the addition of paroxetine 20 mg once daily for 12 days. Dextromethorphan exposure (AUC₀₋₁₂) and C_{max} increased by 1.5 fold and 1.4 fold, respectively, and quinidine exposure (AUC₀₋₁₂) and C_{max} increased by 1.4 fold and 1.3 fold, respectively, and dextrophan exposure (AUC₀₋₁₂) and C_{max} decreased by 14% and 18%, respectively, and paroxetine exposure (AUC₀₋₂₄) and C_{max} increased by 2.3 fold and 2.0 fold, respectively, when paroxetine was added to the combination dose of dextromethorphan/quinidine at steady state (Group 2).

When the combination dose of dextromethorphan/quinidine was added to paroxetine at steady state (Group 1), paroxetine exposure (AUC₀₋₂₄) and C_{max} increased by 1.7 fold and 1.5 fold, respectively, while dextromethorphan and quinidine exposure did not change significantly and dextrophan exposure (AUC₀₋₁₂) and C_{max} decreased by 34% and 33%, respectively.

Based on these results, when dextromethorphan hydrobromide and quinidine sulfate is prescribed with drugs such as paroxetine that inhibit or are extensively metabolized by CYP2D6, consideration should be given to initiating treatment with a lower dose. The dose of paroxetine can then be adjusted based on clinical response; however, dosage above 35 mg/day is not recommended [see Warnings and Precautions (5.4)].

NMDA receptor antagonists (memantine)

A drug interaction study was conducted between a higher combination dose of dextromethorphan/quinidine (dextromethorphan 30 mg/quinidine 30 mg) and memantine 20 mg/day to investigate the potential pharmacodynamic and pharmacokinetic interactions in 52 healthy subjects. Both dextromethorphan and memantine are antagonists of the N-methyl-D-aspartate (NMDA) receptor, which could theoretically result in an additive effect at NMDA receptors and potentially an increased incidence of adverse events. There was no significant difference in the plasma concentrations of dextromethorphan and dextrophan before and after the administration of memantine. Plasma concentrations of quinidine increased 20 to 30% when memantine was added to dextromethorphan 30 mg/quinidine 30 mg.

12.5 Pharmacogenomics

The quinidine component of dextromethorphan hydrobromide and quinidine sulfate is intended to inhibit CYP2D6 so that higher exposure to dextromethorphan can be achieved compared to when dextromethorphan is given alone. Approximately 7 to 10% of Caucasians and 3 to 8% of African Americans generally lack the capacity to metabolize CYP2D6 substrates and are classified as PMs. The quinidine component of dextromethorphan hydrobromide and quinidine sulfate is not expected to contribute to the effectiveness of dextromethorphan hydrobromide and quinidine sulfate in PMs, but adverse events of the quinidine are still possible. In those patients who may be at risk of significant toxicity due to quinidine, genotyping to determine if they are PMs should be considered prior to making the decision to treat with dextromethorphan hydrobromide and quinidine sulfate [see Warnings and Precautions (5.4), (5.8), and Clinical Pharmacology (12.3)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 26-week carcinogenicity study in the Tg.rasH2 transgenic mouse, dextromethorphan and quinidine, alone and in combination, at oral doses up to 100/100 mg/kg/day did not show any evidence of carcinogenic potential.

In a two-year carcinogenicity study in rats, dextromethorphan/quinidine were administered at oral doses of 0/0, 5/100, 20/100, 50/100, 50/0, 0/100 mg/kg/day. No biologically significant tumor findings were observed. The highest dose tested (50/100 mg/kg/day) is approximately 12/50 times the recommended human dose (RHD) of 40/20 mg/day on a mg/m² basis.

Mutagenesis

Dextromethorphan/quinidine was negative in an *in vitro* chromosomal aberration assay in human lymphocytes.

Dextromethorphan was negative in *in vitro* (bacterial reverse mutation, chromosomal aberration in human lymphocytes) and *in vivo* (mouse micronucleus) assays.

Quinidine was negative in an *in vitro* bacterial reverse mutation assay and in an *in vivo* mouse micronucleus assay. Quinidine induced chromosomal aberrations in an *in vitro* chromosomal aberration assay in the presence of metabolic activation.

Impairment of fertility

When dextromethorphan/quinidine was administered orally (0/0, 5/100, 15/100, and 50/100 mg/kg/day) to male and female rats prior to and during mating, and continuing to Day 7 of gestation in females, no effect on fertility was observed up to the highest dose tested, which is approximately 12/50 times the RHD on a mg/m² basis.

14 CLINICAL STUDIES

The efficacy of dextromethorphan hydrobromide and quinidine sulfate was demonstrated in one trial in patients with pseudobulbar affect (PBA). These patients had underlying amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS). Other trials at higher doses (dextromethorphan 30 mg/quinidine 30 mg) provided supportive evidence.

In the dextromethorphan hydrobromide and quinidine sulfate trial, patients with PBA were randomized to receive dextromethorphan hydrobromide and quinidine sulfate dextromethorphan 20 mg/quinidine 10 mg, (N=107), dextromethorphan 30 mg/quinidine 10 mg (N=110), or placebo (N=109) for 12 weeks.

The primary outcome measure, laughing and crying episodes (Figure 1), was statistically significantly lower in each dextromethorphan/quinidine arm compared to placebo, based on an analysis of the sums of the episode counts over the double-blind phase. The secondary endpoint was the Center for Neurologic Studies Laughter Scale (CNS-LS), a seven-item self-report questionnaire with 3 items assessing crying and 4 assessing laughter. CNS-LS was analyzed based on the difference between the mean scores on day 84 and baseline, and was also statistically significantly lower in each dextromethorphan/quinidine arm compared

to placebo (Figure 2). There were no clinically important differences between dextromethorphan hydrobromide and quinidine sulfate and the dextromethorphan 30 mg/quinidine 10 mg arm.

Figure 1: Mean PBA Episode Rates by Visit

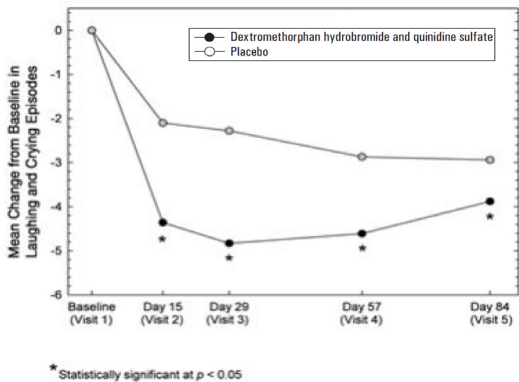
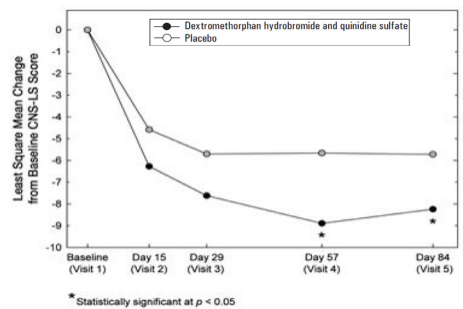


Figure 2: Least Square Mean CNS-LS Scores by Visit



Two additional studies conducted using a higher dose combination of dextromethorphan/quinidine (dextromethorphan 30 mg/quinidine 30 mg) provided supportive evidence of dextromethorphan hydrobromide and quinidine sulfate efficacy. The first was a 4-week study in PBA patients with underlying ALS, and the second was a 12-week study in patients with underlying MS. In both studies, the primary outcome measure, CNS-LS, and the secondary outcome measure, laughing and crying episodes, were statistically significantly decreased by the dextromethorphan/quinidine combination.

16 HOW SUPPLIED/STORAGE AND HANDLING

Dextromethorphan hydrobromide and quinidine sulfate capsules are supplied as white to off-white colored opaque hard gelatin capsule imprinted with 'H' on cap with black ink and 'D22' on body with black ink filled with white to off-white powder. Dextromethorphan hydrobromide and quinidine sulfate capsules are supplied in the following package configuration:

Package Configuration	Capsule Strength (mg)	NDC Code
Bottles of 60 (30 day supply)	dextromethorphan 20 mg/ quinidine 10 mg	31722-693-60

Storage

Store dextromethorphan hydrobromide and quinidine sulfate capsules at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Protect from light and moisture.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity

Patients should be advised that a hypersensitivity reaction to dextromethorphan hydrobromide and quinidine sulfate could occur. Patients should be instructed to seek medical attention immediately if they experience symptoms indicative of hypersensitivity after taking dextromethorphan hydrobromide and quinidine sulfate capsules [see Contraindications (4.2), Warnings and Precautions (5.1)].

Cardiac effects

Patients should be advised to consult their healthcare provider immediately if they feel faint or lose consciousness. Patients should be counseled to inform their healthcare provider if they have any personal or family history of QTc prolongation [see Contraindications (4.4), Warnings and Precautions (5.3), Drug Interactions (7)].

Dizziness

Patients should be advised that dextromethorphan hydrobromide and quinidine sulfate capsules may cause dizziness. Precautions to reduce the risk of falls should be taken, for patients with motor impairment affecting gait or a history of falls [see Warnings and Precautions (5.5), Adverse Reactions (6.1)].

Drug Interactions

Inform patients that dextromethorphan hydrobromide and quinidine sulfate capsules increases the risk of adverse drug interactions. Instruct patients to inform their healthcare provider about all the medications that they are taking before taking dextromethorphan hydrobromide and quinidine sulfate capsules. Before taking any new medications, patients should tell their healthcare provider that they are taking dextromethorphan hydrobromide and quinidine sulfate capsules [see Drug Interactions (7)].

Dosing Instructions

Instruct patients to take dextromethorphan hydrobromide and quinidine sulfate capsules exactly as prescribed. Instruct patients not to take more than 2 capsules in a 24-hour period and to make sure that there is an approximate 12-hour interval between doses, and not to take a double dose after they miss a dose [see Dosage and Administration (2.1)].

General

Patients should not share or give dextromethorphan hydrobromide and quinidine sulfate capsules to others, even if they have the same symptoms, because they may harm them.

Advise patients to contact their healthcare provider if their PBA symptoms persist or worsen.

Advise patients to keep this and all medications out of reach of children and pets.



Manufactured for:
Camber Pharmaceuticals, Inc.,
Piscataway, NJ 08854

by: HETERO™
Hetero Labs Limited
Jeedimidi, Hyderabad - 500 055, India.

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