Summary of Products Characteristics

Product Summary

1. Trade name of the Medical Product

Quinidine sulfate 200 mg

2. Qualitative and Quantitative Composition

Each tablets contains 200 mg of quinidine sulfate

For the full list of excipient, see 6.1

3 . Pharmaceutical Form

Tablet

4. Clinical Particulars

4.1 Therapeutic indications

Treatment of certain cardiac arrhythmias: atrial fibrillation, atrial flutter and ventricular arrhythmias

4.2 Posology and method of administration

- Adult dosage:

For Atrial fibrillation and flutter, Chronic therapy to reduce recurrence: immediate-release tablet, 200 mg ORALLY every 6 h; if needed and patient tolerates, may raise dose cautiously.

For Ventricular arrhythmia, Life-threatening: immediate-release tablet, 200 mg ORALLY every 6 h; if needed and patient tolerates, may raise dose cautiously.

The dosage should be adapted in renal or hepatic insufficiency.

- Children dosage:

Quinidine is not recommended in children.

4.3 Contraindications

Quinidine sulfate should not be given to patients with:

● Hypersensitivity to quinidine or cinchona alkaloids (quinine).

● have developed thrombocytopenic purpura during prior therapy with quinidine or quinine.

Quinidine is also contraindicated in patients who, like those with myasthenia gravis, might be adversely affected by an anticholinergic agent.

In the absence of a functioning artificial pacemaker, quinidine is also contraindicated in any patient whose cardiac rhythm is dependent upon a junctional or idioventricular pacemaker, including patients in complete atrioventricular block.

4.4 Special Warning and Precaution for Use

Mortality

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 flutter/fibrillation, the best available data come from a meta-analysis Pharmacological Properties /Clinical Effects. In the patients studied in the trials there analyzed, the mortality associated with the use of quinidine was more than three times as great as the mortality associated with the use of placebo.

Another meta-analysis, also described under Pharmacological Properties /Clinical Effects, showed that in patients with various non-life-threatening ventricular arrhythmias, the mortality associated with the use of quinidine was consistently greater than that associated with the use of any of a variety of alternative antiarrhythmics.

Pharmacokinetic consideration

Renal or hepatic dysfunction causes the elimination of quinidine to be slowed, while congestive heart failure causes a reduction in quinidine's apparent volume of distribution. Any of these conditions can lead to quinidine toxicity if dosage is not appropriately reduced. In addition, interactions with coadministered drugs can alter the serum concentration and activity of quinidine, leading either to toxicity or to lack of efficacy if the dose of quinidine is not appropriately modified. (See **interactions with other medicaments and other forms of interaction.**)

Proarrhythmic effects

Like many other drugs (including all other class IA antiarrhythmics), quinidine prolongs the QTC interval, and this can lead to *torsades de pointes,* a life-threatening ventricular arrhythmia (see **OVERDOSE**). The risk of *torsades* is increased by bradycardia, hypokalemia, hypomagnesemia, hypocalcemia, or high serum levels of quinidine, but it may appear in the absence of any of these risk factors. The best predictor of this arrhythmia appears to be the length of the QTC interval, and quinidine should be used with extreme care in patients who have preexisting long- QT syndromes, who have histories of *torsades de pointes* of any cause, or who have previously responded to quinidine (or other drugs that prolong ventricular repolarization) with marked lengthening of the QTC interval. Estimation of the incidence of *torsades* in patients with therapeutic levels of quinidine is not possible from the available data. Other ventricular arrhythmias that have been reported with quinidine include frequent extrasystoles, ventricular tachycardia, ventricular flutter, and ventricular fibrillation.

Paradoxical increase in ventricular rate in atrial flutter/fibrillation

When quinidine is administered to patients with atrial flutter/fibrillation, the desired pharmacologic reversion to sinus rhythm may (rarely) be preceded by a slowing of the atrial

rate with a consequent increase in the rate of beats conducted to the ventricles. The resulting ventricular rate may be very high (greater than 200 beats per minute) and poorly tolerated. This hazard may be decreased if partial atrioventricular block is achieved prior to initiation of quinidine therapy, using conduction-reducing drugs such as digitalis, verapamil, diltiazem, or a β-receptor blocking agent.

Exacerbated bradycardia in sick sinus syndrome

In patients with the sick sinus syndrome, quinidine has been associated with marked sinus node depression and bradycardia.

Vagolysis

Because quinidine opposes the atrial and A-V nodal effects of vagal stimulation, physical or pharmacological vagal maneuvers undertaken to terminate paroxysmal supraventricular tachycardia may be ineffective in patients receiving quinidine.

Precautions:

Heart block:

In patients without implanted pacemakers who are at high risk of complete atrioventricular block (*e.g.,* those with digitalis intoxication, second-degree atrioventricular block, or severe intraventricular conduction defects), quinidine should be used only with caution.

Avoid the sun exposure with use of this medicine.

Important information about excipients:

Each tablet contains 31 mg of lactose: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interactions with other Medicaments and other forms of Interaction

The following drug interactions should be considered when prescribing quinidine sulfate.

a) Pharmacokinetic reason:

- Drugs that alkalinize the urine (**carbonic-anhydrase inhibitors (acetazolamide), sodium bicarbonate, thiazide diuretics**) reduce renal elimination of quinidine.

- **Amiodarone or cimetidine**: increase levels of quinidine levels by pharmacokinetic mechanisms that are not well understood

- **Nifedipine**:, decrease quinidine levels by mechanism not understood

- Phenobarbital, phenytoin, Rifampicin: Hepatic elimination of quinidine may be accelerated by coadministration of drugs that induce production of cytochrome P450 3A4.

- Ketaconazole, **Itraconazole, Voriconazole:** quinidine levels rise when coadministered with Ketaconazole, Itraconazole and Voriconazole, Perhaps because of competition for the P450 3A4 metabolic pathway,

- Propranolol: Coadministration of **propranolol** usually does not affect quinidine pharmacokinetics, but in some studies the β-blocker appeared to cause increases in the peak serum levels of quinidine, decreases in quinidine's volume of distribution, and decreases in total quinidine clearance. The effects (if any) of coadministration of **other β-blockers** on quinidine pharmacokinetics have not been adequately studied.

- Diltiazem: significantly decreases the clearance and increases the t1/2 of quinidine, but quinidine does not alter the kinetics of diltiazem.

- Verapamil: Hepatic clearance of quinidine is significantly reduced during coadministration of verapamil, with corresponding increases in serum levels and half-life.

- Digoxin: Quinidine slows the elimination of digoxin and simultaneously reduces digoxin's apparent volume of distribution. As a result, serum digoxin levels may be as much as doubled. When quinidine and digoxin are coadministered, digoxin doses usually need to be reduced. Serum levels of digoxin are also raised when quinidine is coadministered, although the effect appears to be smaller.

- **Warfarin:** quinidine potentiates the anticoagulatory action of warfarin,by a mechanism that is not understood. The anticoagulant dosage may need to be reduced.

Cytochrome P450 2D6 is an enzyme critical to the metabolism of many drugs, notably including **mexiletine**, some **phenothiazines**, and most **polycyclic antidepressants**. Constitutional deficiency of cytochrome P450 2D6 is found in less than 1% of Orientals, in about 2% of American blacks, and in about 8% of American whites. Testing with debrisoquine is sometimes used to distinguish the P450 2D6-deficient "poor metabolizers" from the majority-pheno-type "extensive metabolizers".

When drugs whose metabolism is P450 2D6-dependent are given to poor metabolizers, the serum levels achieved are higher, sometimes much higher, than the serum levels achieved when identical doses are given to extensive metabolizers. To obtain similar clinical benefit without toxicity, doses given to poor metabolizers may need to be greatly reduced. In the cases of prodrugs whose actions are actually mediated by P450 2D6-produced metabolites (for example, **codeine** and **hydrocodone**, whose analgesic and antitussive effects appear to be mediated by morphine and hydromorphone, respectively), it may not be possible to achieve the desired clinical benefits in poor metabolizers.

Quinidine is not metabolized by cytochrome P450IID6, but therapeutic serum levels of quinidine inhibit the action of cytochrome P450IID6, effectively converting extensive metabolizers into poor metabolizers. Caution must be exercised whenever quinidine is prescribed together with drugs metabolized by cytochrome P450 2D6.

- Procainamide: Perhaps by competing for pathways of renal clearance, coadministration of quinidine causes an increase in serum levels of **procainamide**.

- **Haloperidol, Droperidol:** Serum levels are increased when quinidine is coadministered.

- **Aripiprazole**: Concurrent use of ARIPIPRAZOLE and QUINIDINE may result in increased aripiprazole levels.

- Nortriptyline: Concurrent use of NORTRIPTYLINE and QUINIDINE may result in increased nortriptyline plasma concentrations; and increased risk of cardiotoxicity.

- Dihydropyridine calcium-channel blockers: Presumably because both drugs are metabolized by cytochrome P450 2D6, coadministration of quinidine causes variable slowing of the metabolism of nifedipine. Interactions with other dihydropyridine calcium-channel blockers have not been reported, but these agents (including felodipine**,** nicardipine, and

nimodipine) are all dependent upon 3A4 for metabolism, so similar interactions with quinidine should be anticipated.

b) ***pharmacodynamics reason***

Quinidine's anitcholinergic, vasodilating, and negative inotropic actions may be additive to those of other drugs with these effects, and antagonistic to those of drugs with cholinergic, vasoconstricting, and positive inotropic effects. For example, when quinidine and **verapamil** are coadministered in doses that are each well tolerated as monotherapy, hypotension attributable to additive peripheral α-blockade is sometimes reported.

Quinidine potentiates the actions of depolarizing (succinylcholine, decamethonium) and nondepolarizing (*d*-tubocurarine, pancuronium) **neuromuscular blockingagents**. These phenomena are not well understood, but they are observed in animal models as well as in humans. In addition, *in vitro* addition of quinidine to the serum of pregnant women reduces the activity of pseudocholinesterase, an enzyme that is essential to the metabolism of succinylcholine.

- **HIV protease inhibitors** eg indinavir, ritonavir, nelfinavir: Concurrent use of QUINIDINE and HIV protease inhibitors may result in an increased risk of quinidine toxicity (ventricular arrhythmias, hypotension, exacerbation of heart failure).

- Dofetilide, astemizole, cisapride, Pimozide, a**ntibiotic of macrolide group (such erythromycin),** ketolide antibiotics (eg, telithromycin), **risperidone, norepinephrine reuptake inhibitors**: Concurrent use of their medicines and QUINIDINE may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).

- Mefloquine: Concurrent use of MEFLOQUINE and QUINIDINE may result in increased risk of QT prolongation

- **Amiloride**: Concurrent use of AMILORIDE and QUINIDINE may result in an increased risk of arrhythmias in patients with ventricular tachycardia.

- Procainamide: Concurrent use of QUINIDINE and PROCAINAMIDE may result in hypotension and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).

Non-interactions of quinidine with other drugs

Quinidine has no clinically significant effect on the pharmacokinetics of **diltiazem, flecainide, mephenytoin, metoprolol, propafenone, propranolol, quinine, timolol,** or **tocainide**.

Conversely, the pharmacokinetics of quinidine are not significantly affected by **caffeine, ciprofloxacin, digoxin, digitoxin, diltiazem, felodipine, terfenadine omeprazole,** or **quinine.**

Quinidine's pharmacokinetics are also unaffected by cigarette smoking

4.6 Fertility, pregnancy and lactation

Quinidine is classified in category C by U.S. Food and Drug Administration's Pregnancy.

a) Pregnancy:

Animal reproductive studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidine should be given to a pregnant woman only if clearly needed.

Human placental transport of quinidine has not been systematically studied. In one neonate whose mother had received quinidine throughout her pregnancy, the serum level of quinidine was equal to that of the mother, with no apparent ill effect. The level of quinidine in amniotic fluid was about three times higher than that found in serum. In another case, the levels of quinidine and 3-hydroxyquinidine in cord blood were about 30% of simultaneous maternal levels.

Labor and Delivery

Quinine is said to be oxytocic in humans, but there are no adequate data as to quinidine's effects (if any) on human labor and delivery.

b) Lactation:

Quinidine is present in human milk at levels slightly lower than those in maternal serum; a human infant ingesting such milk should (scaling directly by weight) be expected to develop serum quinidine 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, and neonates' reduced protein binding of quinidine may increase their risk of toxicity at low total serum levels. Administration of quinidine should (if possible) be avoided in lactating women who continue to nurse.

c) Fertility:

There are no animal data as to quinidine's potential to impair fertility.

4.7 Effects on Ability to Drive and Use Machines

Quinidine may impair the mental and/or physical abilities (dizziness or blurred vision) required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Patients should be advised to make sure they are not affected before undertaking any potentially hazardous tasks.

4.8 Undesirable Effects

Quinidine preparations have been used for many years, but there are only sparse data from which to estimate the incidence of various adverse reactions. The adverse reactions most frequently reported have consistently been gastrointestinal, including diarrhea, nausea, vomiting, and heartburn/esophagitis. In one study of 245 adult outpatients who received quinidine to suppress premature ventricular contractions, the incidences of reported adverse experiences were as shown in the table below. The most serious quinidine-associated adverse reactions are described above under **Special Warning and Precaution for Use**

Adverse Experiences in a 245-Patient PVC Trial	
	Incidence (%)
diarrhea	85 (35)
"upper gastrointestinal distress"	55 (22)

lightheadedness	37 (15)
headache	18 (7)
fatigue	17 (7)
palpitations	16 (7)
angina-like pain	14 (6)
weakness	13 (5)
rash	11 (5)
visual problems	8 (3)
change in sleep habits	7 (3)
tremor	6 (2)
nervousness	5 (2)
discoordination	3 (1)

Vomiting and diarrhea can occur as isolated 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, deafness, vertigo, blurred vision, diplopia, photophobia, headache, confusion, and delirium.

Cinchonism is most often a sign of chronic quinidine toxicity, but it may appear in sensitive patients after a single moderate dose.

A few cases of **hepatotoxicity**, including granulomatous hepatitis, have been reported in patients receiving quinidine. All of these have appeared during the first few weeks of therapy, and most (not all) have remitted once quinidine was withdrawn.

Autoimmune and inflammatory syndromes associated with quinidine therapy have included fever, urticaria, flushing, exfoliative rash, bronchospasm, psoriaform rash, pruritus and lymphadenopathy, hemolytic anemia, vasculitis, pneumonitis, thrombocytopenic purpura, uveitis, angioedema, agranulocytosis, the sicca syndrome, arthralgia, myalgia, elevation in serum levels of skeletal-muscle enzymes, and a disorder resembling systemic lupus erythematosus.

Convulsions, apprehension, and ataxia have been reported, but it is not clear that these were not simply the results of hypotension and consequent cerebral hypoperfusion. There are many reports of syncope. Acute psychotic reactions have been reported to follow the first dose of quinidine, but these reactions appear to be extremely rare.

Other adverse reactions occasionally reported include depression, mydriasis, disturbed color perception, night blindness, scotomata, optic neuritis, visual field loss, photosensitivity, and abnormalities of pigmentation.

4.9 Overdose

Overdoses with various oral formulations of quinidine have been well described. Death has been described after a 5-gram ingestion by a toddler, while an adolescent was reported to survive after ingesting 8 grams of quinidine.
The most important ill effects of acute quinidine overdoses are ventricular arrhythmias and hypotension. Other signs and symptoms of overdose may include vomiting, diarrhea, tinnitus, high-frequency hearing loss, vertigo, blurred vision, diplopia, photophobia, headache, confusion, and delirium.

Arrhythmias

Serum quinidine levels can be conveniently assayed and monitored, but the electrocardiographic QTC interval is a better predictor of quinidine-induced ventricular arrhythmias.

The necessary treatment of hemodynamically unstable polymorphic ventricular tachycardia (including *torsades de pointes*) is withdrawal of treatment with quinidine and 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.

Quinidine-associated ventricular tachyarrhythmias with normal underlying QTC intervals have not been adequately studied. Because of the theoretical possibility of QT-prolonging effects that might be additive to those of quinidine, other antiarrhythmic with Class I (disopyramide, procainamide) or Class III activities should (if possible) be avoided.

Similarly, although the use of bretylium in quinidine overdose has not been reported, it is reasonable to expect that the α-blocking properties of bretylium might be additive to those of quinidine, resulting in problematic hypotension.

If the post-cardioversion QTC interval is prolonged, then the pre-cardioversion polymorphic ventricular tachyarrhythmia was (by definition) *torsades depointes*. In this case, lidocaine and bretylium are unlikely to be of value, and other Class I antiarrhythmic (disopyramide, procainamide) are likely to exacerbate the situation. Factors contributing to QTC prolongation (especially hypokalemia, hypomagnesemia, and hypocalcemia) should be sought out and (if possible) aggressively corrected.

Prevention of recurrent *torsades* may require sustained overdrive pacing or the cautious administration of isoproterenol (30 to 150 ng/kg/min).

Hypotension

Quinidine-induced hypotension that is not due to an arrhythmia is likely to be a consequence of quinidine-related α-blockade and vasorelaxation. Simple 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 α-agonist catecholamines (norepinephrine, metaraminol) and the Military Anti-Shock Trousers.

Treatment

To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison-Control Center. Telephone numbers of certified poison-control centers are listed in the *Physicians' Desk Reference(PDR)*. In managing overdose, consider the possibilities of multiple-drug overdoses, drug-drug interactions, and unusual drug kinetics in your patient.

Accelerated removal

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 usually removed from the circulation by dialysis.

Following quinidine overdose, drugs that delay elimination of quinidine (cimetidine, carbonicanhydrase inhibitors, thiazide diuretics) should be withdrawn unless absolutely required.

Pharmacological Properties

5.1 Pharmacodynamic properties

Quinidine is an antiarrhythmic agent with class 1A activity.

In cardiac muscle and in Purkinje fibers, quinidine depresses the rapid inward depolarizing sodium current, thereby slowing phase-0 depolarization and reducing the amplitude of the action potential without affecting the resting potential. In normal Purkinje fibers, it reduces the slope of phase-4 depolarization, shifting the threshold voltage upward toward zero. The result is slowed conduction and reduced automaticity in all parts of the heart, with increase of the effective refractory period relative to the duration of the action potential in the atria, ventricles, and Purkinje tissues. Quinidine also raises the fibrillation thresholds of the atria and ventricles, and it raises the ventricular *de*fibrillation threshold as well. Quinidine's actions fall into class 1A in the Vaughan-Williams classification.

By slowing conduction and prolonging the effective refractory period, quinidine can interrupt or prevent reentrant arrhythmias and arrhythmias due to increased automaticity, including atrial flutter, atrial fibrillation, and paroxysmal supraventricular tachycardia. In patients with the sick sinus syndrome, quinidine can cause marked sinus node depression and bradycardia. In most patients, however, use of quinidine is associated with an increase in the sinus rate.

Quinidine prolongs the QT interval in a dose-related fashion. This may lead to increased ventricular automaticity and polymorphic ventricular tachycardias, including *torsades de pointes* (see **Special Warning and Precaution for Use)**

In addition, quinidine has anticholinergic activity, it has negative inotropic activity, and it acts peripherally as an α-adrenergic antagonist (that is, as a vasodilator).

Clinical Effects

Maintenance of sinus rhythm after conversion from atrial fibrillation:

In six clinical trials (published between 1970 and 1984) with a total of 808 patients, quinidine (418 patients) was compared to nontreatment (258 patients) or placebo (132 patients) for the maintenance of sinus rhythm after cardioversion from chronic atrial fibrillation. Quinidine was consistently more efficacious in maintaining sinus rhythm, but a metaanalysis found that mortality in the quinidine-exposed patients (2.9%) was significantly greater than mortality in the patients who had not been treated with active drug (0.8%). Suppression of atrial fibrillation with quinidine has theoretical patient benefits (*e.g.,*improved exercise tolerance; reduction in hospitalization for cardioversion; lack of arrhythmiarelated palpitations, dyspnea, and chest pain; reduced incidence of systemic embolism and/or stroke), but these benefits have never been demonstrated in clinical trials. Some of these benefits (*e.g.,* reduction in stroke incidence) may be achievable by other means (anticoagulation).

By slowing the rate of atrial flutter/fibrillation, quinidine can decrease the degree of atrioventricular block and cause an increase, sometimes marked, in the rate at which supraventricular impulses are successfully conducted by the atrioventricular node, with a

resultant paradoxical increase in ventricular rate (see **Special Warning and Precaution for Use**).

Non-life-threatening ventricular arrhythmias:

In studies of patients with a variety of ventricular arrhythmias (mainly frequent ventricular premature beats and non-sustained ventricular tachycardia), quinidine (total N=502) has been compared to flecainide (N=141), mexiletine (N=246), propafenone (N=53), and tocainide (N=67). In each of these studies, the mortality in the quinidine group was numerically greater than the mortality in the comparator group. When the studies were combined in a metaanalysis, quinidine was associated with a statistically significant threefold relative risk of death.

At therapeutic doses, quinidine's only consistent effect upon the surface electrocardiogram is an increase in the QT interval. This prolongation can be monitored as a guide to safety, and it may provide better guidance than serum drug levels (**Special Warning and Precaution for Use**).

5.2 Pharmacokinetic properties

The absolute bioavailability of quinidine from quinidine sulfate tablets is about 70%, but this varies widely (45 to 100%) between patients. The less-than-complete bioavailability is the result of first-pass metabolism in the liver. Peak serum levels generally appear about 2 hours after dosing; the rate of absorption is somewhat slowed when the drug is taken with food, but the extent of absorption is not changed.

The **volume of distribution** of quinidine is 2 to 3 L/kg in healthy young adults, but this may be reduced to as little as 0.5 L/kg in patients with congestive heart failure, or increased to 3 to 5 L/kg in patients with cirrhosis of the liver. At concentrations of 2 to 5 mg/L (6.5 to 16.2 µmol/L), the fraction of quinidine bound to plasma proteins (mainly to α1-acid glycoprotein and to albumin) is 80 to 88% in adults and older children, but it is lower in pregnant women, and in infants and neonates it may be as low as 50 to 70%. Because α1-acid glycoprotein levels are increased in response to stress, serum levels of total quinidine may be greatly increased in settings such as acute myocardial infarction, even though the serum content of unbound (active) drug may remain normal. Protein binding is also increased in chronic renal failure, but binding abruptly descends toward or below normal when heparin is administered for hemodialysis.

Quinidine **clearance** typically proceeds at 3 to 5 mL/min/kg in adults, but clearance in children may be twice or three times as rapid. The elimination half-life is 6 to 8 hours in adults and 3 to 4 hours in children. Quinidine clearance is unaffected by hepatic cirrhosis, so the increased volume of distribution seen in cirrhosis leads to a proportionate increase in the elimination half-life.

Most quinidine is eliminated hepatically via the action of cytochrome P450 3A4; there are several different hydroxylated metabolites, and some of these have antiarrhythmic activity.

The most important of quinidine's metabolites is 3-hydroxyquinidine (3HQ), serum levels of which can exceed those of quinidine in patients receiving conventional doses of quinidine sulfate. The volume of distribution of 3HQ appears to be larger than that of quinidine, and the elimination half-life of 3HQ is about 12 hours.

As measured by antiarrhythmic effects in animals, by QTc prolongation in human volunteers, or by various *in vitro* techniques, 3HQ has at least half the antiarrhythmic activity of the parent compound, so it may be responsible for a substantial fraction of the effect of quinidine sulfate in chronic use.

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. The net renal clearance is about 1 mL/min/kg in healthy adults. When renal function is taken into account, quinidine clearance is apparently independent of patient age.

5.3 Preclinical safety data

Not applicable.

Pharmaceutical Particulars

6.1 List of excipients

Starch, Talc, Lactose DC., Magnesium stearate, Gelatin, Acacia,

6.2 Incompatibilities

6.3 Shelf-life

Shelf-life
Three years from the date of manufacture.

Shelf-life after dilution/reconstitution
Not applicable.

Shelf-life after first opening
Not applicable.

6.4 Special precautions for storage

Store below 25°C in a dry place.

6.5 Nature and contents of container

Blister PVC-ALU

Pack size: 30 tablets

Administrative Data

7 Manufacturer
Rekah Pharmaceutical industry LDT,
30 hamelacha st. Holon 58859, Israel

8 License Holder and Importer:
Rekah Pharmaceutical industry LDT,
30 hamelacha st. Holon 58859, Israel

9. License numbers

023-85-20912-00

9 Date of First Authorisation/Renewal of Authorisation
May 2014