Dofetilide is a new antiarrhythmic drug that recently was recommended for approval by an advisory committee to the Food and Drug Administration (FDA) for treatment of patients with persistent atrial fibrillation. Dofetilide is a specific blocker of the rapid component of the outward delayed rectifier potassium current $I_{Kr}$ and will represent the first drug with relatively pure class III antiarrhythmic properties to be widely released.

Basic Electrophysiology

Cardiac depolarization results principally from the flow of inward Na$^+$ and Ca$^{2+}$ ions as the rapid and slow inward currents. Repolarization results from a balance between inactivation of the slow inward current and activation of repolarizing predominantly K$^+$ currents. Early repolarization results from a transient outward current, $I_{To}$, which is activated rapidly by membrane depolarization. Terminal repolarization is mediated by outward delayed rectifier K$^+$ currents, $I_{Ks}$, which are activated slowly (over a period of 200 to 300 ms) on membrane depolarization and turn off, or deactivate, relatively slowly on membrane repolarization.

$I_{Kr}$ can be separated pharmacologically into 2 components: a rapidly activating component, $I_{Kr,a}$, and a slower component, $I_{Kr,s}$, each carried by a separate ion channel molecule. HERG channels are responsible for $I_{Kr,a}$, whereas $I_{Kr,s}$ flows through KvLQT1 channels. Specific blockers of $I_{Kr,s}$ are therefore classified as pure class III antiarrhythmic agents because they produce only prolongation of action potential duration (and hence of QT interval). These actions may result in arrhythmia termination or suppression but can also lead to excess QT prolongation and polymorphic ventricular tachycardia. Examples of specific $I_{Kr}$ blockers include the methanesulfonanilide agents dofetilide, E4031, almokalant, and D-sotalol.

Effects of Dofetilide on $I_{Kr}$

Dofetilide blocks $I_{Kr}$ in all myocardial tissues with high potency (50% effective concentration [EC50] in the nanomolar range). Block is voltage dependent and most prominent at depolarized potentials. It does not occur in resting muscle but rather develops on depolarization. Recovery from block is also potential dependent and is very slow at hyperpolarized potentials close to the resting potential. Steady-state block at any dose is constant and does not change with increasing heart rate because the recovery time is much greater than the diastolic interval.

Dofetilide block of $I_{Kr}$ increases as extracellular potassium concentration ([K]o) is reduced. This sensitivity of dofetilide block to [K]o is of obvious clinical importance. Even moderate hypokalemia would be expected to disproportionately increase action potential prolongation induced by dofetilide, and correction of hypokalemia is of crucial importance in treating QT prolongation and torsade de pointes caused by $I_{Kr}$ blockade. Conversely, hyperkalemia blunts the effect of dofetilide, suggesting the possibility of reduced efficacy after acute coronary occlusion or during rapid heart rates, when local cardiac tissue hyperkalemia may occur.

Blockade of $I_{Kr}$ by dofetilide is rate independent, but in intact cells and in the intact heart, the effects of dofetilide to prolong action potential duration and QT interval diminish as heart rate increases; so, in practice, the drug exhibits reverse use dependence. This results from rate-induced enhancement of other repolarizing ionic currents (principally $I_{Ks}$) that partially offset the effect of dofetilide and accumulation of K$^+$ in intracellular clefts, which reduces $I_{Kr}$ blockade by dofetilide and enhances the magnitude of $I_{Kr}$.6,8

Effects of Dofetilide on Action Potential Duration

Blockade of $I_{Kr}$ results in a dose-dependent prolongation of action potential duration. In isolated myocardium, maximal prolongation of action potential duration is $\approx 50\%$, and this is paralleled by a similar prolongation of the effective refractory period. Dofetilide is more potent in isolated Purkinje fibers, where the EC50 is 10-fold lower than in ventricle. Similar prolongations of action potential duration (or QT interval) and effective refractory period have been reported in intact animals and in humans.

In isolated atrial myocardium, the action of dofetilide to prolong action potential duration and effective refractory period was more than double that of ventricle. The clinical significance of this difference is not clear, however, because human monophasic action potential duration and effective refractory period prolongation by dofetilide were identical in atrium and ventricle.

Dofetilide reduced spontaneous heart rate and prolonged sinus node recovery time in isolated atria. In isolated sino-atrial node cells, dofetilide-induced inhibition of $I_{Kr}$ resulted in a reduction in the slope of the pacemaker potential...
and reduced the maximum diastolic potential. This may cause sinus slowing or arrest at concentrations higher than those expected during clinical use.\textsuperscript{12–15,20–22}

The effects of dofetilide on action potential duration were preserved in endocardial specimens of human ventricular myocardium obtained from explanted human hearts with dilated or ischemic cardiomyopathy.\textsuperscript{23} Dofetilide had similar effects on action potential duration in normal and hypertrophied rabbit hearts,\textsuperscript{24} and the effect of dofetilide was not affected by simulated metabolic acidosis.\textsuperscript{25} Hypoxia-induced electromechanical changes in ventricular myocardium, including a reduction in developed force and abbreviation of action potential duration, were reversed by dofetilide. These effects are mediated in part by activation of $I_{\text{KATP}}$ channels, but reversal of hypoxic effects was the result of $I_{\text{Ks}}$ blockade, not blockade of the $I_{\text{KATP}}$ channels.\textsuperscript{26} $I_{\text{KATP}}$ channels are thought to play a role in ischemic preconditioning and, interestingly, indirect reversal of the electromechanical effects of stimulation of $I_{\text{KATP}}$ channels by dofetilide does not diminish ischemic preconditioning.\textsuperscript{27,28}

Dofetilide-induced action potential prolongation is blocked by $\beta$-adrenergic stimulation.\textsuperscript{29} This results from adrenergic enhancement of $I_{\text{Ks}}$, which shortens action potential duration.\textsuperscript{30,31}

Reverse Use-Dependence

The decline of class III antiarrhythmic action as heart rate increases, or reverse use-dependence, is theoretically an undesirable feature in an agent used in patients with atrial fibrillation, in which enhanced effects at high heart rates would be preferable. Dofetilide exhibits reverse use-dependence, with rate-related reductions in its capacity to prolong action potential duration and effective refractory period.

Reverse use-dependence of the effect of dofetilide on action potential duration has been demonstrated in multiple cardiac tissues. In guinea pig and canine ventricle, dofetilide-induced prolongation of action potential duration was inhibited as stimulation frequency was increased from 0.5 to 2 Hz, and this trend was much more obvious at 5 Hz.\textsuperscript{9,10} An increase in the dofetilide dose was accompanied by enhancement of reverse use-dependence.\textsuperscript{9} Reverse use-dependence in isolated ventricle was diminished after coadministration of diltiazem. This shortened action potential duration at low heart rates but was without effect at higher rates (3 Hz), resulting in a similar degree of dofetilide-induced action potential lengthening over a wide range of rates.\textsuperscript{32} Conversely, cellular calcium loading either by enhancing L-type calcium currents or by blockade of the Na/K ATPase increased reverse use-dependence through selective prolongation of the action potential at low heart rates.\textsuperscript{32} This would be expected to worsen proarrhythmia.

For similar R-R intervals, dofetilide produces more QT prolongation during sustained slow heart rates than during extrastimuli.\textsuperscript{33} suggesting that potentially proarrhythmic QT prolongation may be more of a problem during sustained bradycardia than after single extra beats with long coupling intervals. Reverse use-dependence may be more significant in atrial tissue. In isolated canine atria, dofetilide was without significant effect at stimulation frequencies of $>3$ Hz,\textsuperscript{28} and in ferret atrial trabeculae a blunted dofetilide-induced prolongation of atrial effective refractory period persisted at 4 Hz.\textsuperscript{18}

Reverse use-dependence is significant in human hearts in vivo over a physiological range of heart rates and dofetilide doses. The relation between R-R interval and QT interval was steeper in patients receiving dofetilide than in control subjects, so that at shorter R-R intervals the degree of drug-induced QT prolongation was smaller.\textsuperscript{34} Similarly, during exercise testing, although dofetilide prolonged QT interval at low heart rates, as rate was increased to 150 per minute, the drug was without effect on QT interval even at high doses.\textsuperscript{35}

Effects of Dofetilide on Arrhythmias in Animal Models

Class III agents would be expected to be more effective in reentrant arrhythmias than, for example, in triggered or automatic rhythms, since their mechanism of action is to prolong refractoriness and wavelength, thus inhibiting reentry. In a chronic myocardial infarction model, dofetilide reduced the induction rate of sustained monomorphic ventricular tachycardia\textsuperscript{14,15,36} and increased the cycle length of induced ventricular tachycardia.\textsuperscript{15} Consistent with its mode of action, however, it did not reduce the incidence of ventricular fibrillation when this was the only inducible ventricular arrhythmia.\textsuperscript{14,36} In a canine model of atrial flutter, dofetilide was more effective than quinidine in slowing and terminating the arrhythmia, an effect that was attributed to drug-induced prolongation of wavelength.\textsuperscript{37} In a model of acute ischemia, dofetilide reduced the incidence of spontaneous ventricular fibrillation.\textsuperscript{13}

Dofetilide reduced dispersion of repolarization in normal animals\textsuperscript{38} but had no effect on dispersion of repolarization in a canine myocardial infarction model\textsuperscript{39} or in a rabbit model of left ventricular hypertrophy.\textsuperscript{40} In patients with stable angina or ventricular tachycardia, dispersion of repolarization was not affected by dofetilide.\textsuperscript{16,17}

Pharmacokinetics

Dofetilide is well absorbed after oral administration, with an absolute bioavailability of $>90$%.\textsuperscript{41–44} Ingestion with food delays absorption but does not affect total bioavailability. Peak plasma concentrations are seen 2 to 3 hours after ingestion in fasted subjects. Plasma protein binding is 60% to 70% at all concentrations. Approximately 70% to 80% of absorbed dofetilide is excreted as unchanged drug by the kidney by active secretion out of the proximal tubule by an organic cation transport mechanism. Hepatic metabolism accounts for 20% to 30% of dofetilide elimination in individuals with normal renal function. Dofetilide is metabolized by CYP3A4 to a mixture of inactive polar metabolites that are then excreted by the kidney.\textsuperscript{45} The terminal elimination half-life is 8 to 10 hours. Total dofetilide clearance in patients without severe renal insufficiency is proportional to creatinine clearance. On the basis of data from clinical trials, it is recommended that dofetilide dosage be adjusted according to creatinine clearance estimated by the Cockcroft and Gault equation

$$[\text{Creatinine clearance (male)}] = (140 - \text{age in years}) \times \text{serum creatinine (milli-}$$
of dofetilide, and this interaction may become significant in patients with renal dysfunction.45 Pharmacodynamic interactions are also possible. Diuretics or other agents causing hypokalemia or agents that produce significant bradycardia would be expected to increase the potential for proarrhythmia.

Clinical Studies
When administered to patients undergoing electrophysiological studies,19,47–49 the primary effects of dofetilide are seen on the refractory periods of atrial and ventricular muscle. Dofetilide has no effect on PR, QRS, or HV intervals. The QT interval and the functional and effective refractory periods of atrial and ventricular muscle are prolonged in a dose-dependent fashion. The correlation between change in QTc interval and plasma dofetilide concentration is essentially linear over a concentration range of 0 to 7 ng/mL.44 Similarly, mean change in QTc correlates well with efficacy in patients with atrial fibrillation.

The majority of the clinical trials with dofetilide have as yet only been published in preliminary form, described in the package insert,44 or presented to an open meeting of the Cardio-Renal Advisory Committee of the FDA held on January 28, 1999.50a Release of a drug after government review publication of the data are an emerging paradigm in drug development.

Supraventricular Arrhythmias
Several groups have studied the ability of intravenous dofetilide to convert sustained episodes of atrial fibrillation and atrial flutter. Falk et al50b randomized 91 patients with sustained atrial fibrillation (75 patients) or atrial flutter (16 patients) to receive either placebo or 1 of 2 doses (4 or 8 μg/kg) of dofetilide. Pharmacological conversion within 4 hours was observed in 31%, 12.5%, and 0% of the high-dose, low-dose, and placebo groups. Conversion was more frequent in the small group with atrial flutter compared with those with atrial fibrillation (54% versus 12.5%) overall. In a similar study, Nørgaard et al51 studied the efficacy of 8 μg/kg of dofetilide for acute conversion of atrial fibrillation and atrial flutter of up to 6 months’ duration. Pharmacological conversion to sinus rhythm was seen in 64% of those with atrial flutter and in 30% of those with atrial fibrillation treated with dofetilide in contrast to 0% and 4% in the placebo group with these two arrhythmias (P<0.006). Frost et al52 studied intravenous dofetilide in 98 patients with atrial fibrillation or atrial flutter in the early period after coronary artery bypass surgery. Dofetilide doses were 4 or 8 μg/kg. Conversion within 3 hours was observed in 44% of the high-dose group, 36% of the low-dose group, and 24% of the placebo group. These differences were not statistically significant.

Two large randomized clinical trials in patients with persistent atrial fibrillation provided the major efficacy data that led to the preliminary approval of dofetilide in the United States. In the Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) trial,44 325 patients with persistent atrial fibrillation were hospitalized and randomized to therapy with either placebo or dofetilide at 1 of 3 doses: 125 μg BID, 250 μg BID, and 500 μg BID. After initial assignment to a dosage group, the actual dose could then be adjusted on the basis of estimated creatinine clearance. Patients with a creatinine clearance >60 mL/min received the assigned dose, whereas patients with a creatinine clearance between 40 and 60 mL/min received one-half the assigned dose. Patients were monitored continuously during the initiation phase, and if they were still in atrial fibrillation after 5 doses of study drug, they underwent DC cardioversion. Patients who converted to and maintained sinus rhythm for 24 hours then entered a maintenance phase. Dofetilide dosage could be adjusted downward the QT or QTc interval increased by >15% to <25% over baseline. If at any time during the study the QT or QTc exceeded 550 ms, dofetilide was discontinued. Repeat cardioversions on therapy were not permitted. The primary end point of the study was the proportion of patients remaining in sinus rhythm on therapy at 6 months. During the initial phase, pharmacological cardioversion occurred in 1.2%, 6.1%, 9.8%, and 29.9% of patients in the placebo, 125 μg BID, 250 μg BID, and 500 μg BID groups, respectively. After pharmacological or electrical conversion, 250 of 350 patients, between 73% and 81% from each group, went on to maintenance therapy. An intention-to-treat analysis for all patients showed the dofetilide 500 μg BID dose superior to placebo, with 50% and 47% of patients in that group still in sinus rhythm at 6 and 12 months, respectively, compared with 30% and 20% of placebo-treated patients at the same time points (P=0.05 and P=0.008). The lower dofetilide dose groups showed less marked effects that did not reach statistical significance. If one includes only patients who entered the maintenance phase, the 500 μg BID dose group was again superior to placebo after both 6 and 12 months (62% and 58% in sinus rhythm on dofetilide versus 37% and 25% in sinus rhythm on placebo). The lower doses of dofetilide did not show a statistically significant difference from placebo.

The European and Australian Multicenter Evaluative Research on Atrial Fibrillation Dofetilide (EMERALD) study44 was a randomized, double-blind, placebo-controlled trial in patients with persistent atrial fibrillation. As in SAFIRE-D, there was both a conversion phase and a maintenance phase. Patients were randomized to receive either placebo, 1 of 3 doses of dofetilide (125, 250, or 500 μg BID), or sotalol 80 mg BID. Downward dosage adjustment was allowed, based on estimated creatinine clearance with a single daily dosage of the original amount used rather than twice-daily dosage for patients with a creatinine clearance between 40 and 60 mL/min. Patients with a creatinine clearance <40 mL/min
were excluded from participation. Five hundred forty-six patients were entered into the conversion phase of the study. Pharmacological conversion was noted in 5.9%, 10.5%, and 29.5% of patients on the 3 ascending doses of dofetilide, in 5.1% of those randomized to sotalol, and in 1.5% of the placebo group. Between 76% and 90% of patients in the 5 groups achieved sinus rhythm after either pharmacological or electrical cardioversion and entered the maintenance portion of the study. Life-table analysis showed a beneficial antiarrhythmic effect on the 3 doses of dofetilide. At 1 year, the specified primary end point of the study, 30%, 45%, and 51% of the 125 μg BID, 250 μg BID, and 500 μg BID dofetilide groups, 38% of the sotalol group, and 16% of the placebo group remained in sinus rhythm, free of recurrent atrial fibrillation. All of the active drug groups were statistically different from placebo.

In contrast to these results in patients with persistent atrial fibrillation, a number of unpublished studies included in the sponsor’s presentation to the FDA showed a nonsignificant but favorable trend among patients with paroxysmal atrial fibrillation. These studies tested doses between 250 mg BID and 750 mg BID and used end points of time to first recurrence and life-table analyses of proportion free of recurrent symptomatic arrhythmia. Further studies in patients with paroxysmal atrial fibrillation are indicated.

Sixteen percent of patients (506 of 3028) entered into the Danish Investigations on Arrhythmia and Mortality on Dofetilide study (DIAMOND, see below) had persistent atrial fibrillation at study entry. The outcomes in these patients and the risk of development of atrial fibrillation among these patients in sinus rhythm initially were analyzed as part of a DIAMOND substudy. All patients were randomly assigned to receive dofetilide or placebo. By protocol, all patients in DIAMOND with atrial fibrillation received 250 mg BID. Patients with persistent atrial fibrillation at entry were followed on their assigned therapy for 1 month. If they remained in atrial fibrillation, they were eligible for cardioversion after an appropriate period of anticoagulation. During the first 30 days of treatment, 56 of 249 patients taking dofetilide versus 7 of 257 patients receiving placebo converted to sinus rhythm. An additional 50 dofetilide patients and 28 placebo patients were electrically cardioverted. Among these patients in whom sinus rhythm was restored, 35% of dofetilide patients versus 84% of placebo-treated patients relapsed into atrial fibrillation. Dofetilide therapy in patients with atrial fibrillation was associated with a lower risk of hospitalization for heart failure–related causes. Among those patients who were originally in sinus rhythm, the dofetilide group also had a lower incidence of new onset of atrial fibrillation (2.0% versus 10.5%, P<0.001). These data support a role for dofetilide in patients with advanced heart disease and atrial fibrillation, but because atrial fibrillation was not used to stratify randomization, they are less conclusive than data from the SAFIRE-D and EMERALD studies.

Ventricular Arrhythmias and Mortality Trials

The DIAMOND trials were double-blind, placebo-controlled trials designed to evaluate the efficacy and safety of dofetilide in high-risk patients with either congestive heart failure (DIAMOND-CHF) or recent myocardial infarction (DIAMOND-MI). These were mortality trials, and specific antiarrhythmic effects were not primary end points. DIAMOND-CHF randomized 1518 patients with abnormal left ventricular function defined echocardiographically as a wall motion index of <1.2 (equivalent to a left ventricular ejection fraction ≤35%). DIAMOND-MI randomized 1510 patients who had had a myocardial infarction within the previous 7 days and had a wall motion index ≤1.2. Patients in both studies were randomized to either dofetilide 500 μg BID or to matching placebo. Patients with atrial fibrillation or flutter by protocol received half the normal dose, namely, 250 μg BID. Downward dosage adjustment was permitted for patients with reduced creatinine clearance and for QT prolongation.

Analysis of total mortality was performed with the use of an intention-to-treat approach. In DIAMOND-CHF, 311 of 762 (41%) dofetilide group patients died compared with 317 of 756 (42%) placebo group patients. In DIAMOND-MI, 230 of 749 (31%) dofetilide group patients and 243 of 761 (32%) placebo group patients died. In both studies, these differences in total mortality rates were not significantly different.

Dofetilide has also been studied in patients with a history of sustained ventricular tachycardia or cardiac arrest. In a small dose-ranging study, Echt et al reported the results of an intravenous dose-ranging study in 41 patients with inducible sustained monomorphic ventricular tachycardia. Among the 41 patients treated with 3.0 to 15.0 μg/kg, 17 had suppression of their inducible arrhythmia. In a multicenter trial, 174 patients with implantable cardioverter-defibrillators (ICDs) were randomly assigned to receive either 500 μg BID dofetilide or placebo. Dofetilide resulted in nonsignificant increases in median time to first all-cause ICD shock (hazard ratio 0.67, P=0.07) and first appropriate shock (hazard ratio 0.73, P=0.24) but no change in total appropriate ICD therapy episodes including both shocks and antitachycardia pacing. Although further long-term studies with dofetilide in patients with prior sustained ventricular arrhythmias will no doubt be conducted, at present no study indicates long-term benefit from dofetilide in these patients.

Safety

In placebo-controlled trials, the incidence of noncardiac adverse events in the patients on dofetilide has been similar to that in the placebo groups. The major cardiovascular adverse events have been directly related to the electrophysiological properties of the drug: QT prolongation and torsade de pointes.

Before 1994, patients participating in clinical trials involving dofetilide were assigned doses without regard to baseline creatinine clearance, and doses up to 750 mg BID were allowed. After a number of cases of torsade de pointes, late studies estimated baseline creatinine clearance by use of the equation:

\[
\text{Creatinine clearance (male)} = \frac{(140-\text{age in years}) \times \text{body weight in kilograms}}{72 \times \text{serum creatinine (milligrams per 100 mL)}}
\]

and:

\[
\text{Creatinine clearance (female)} = \frac{(140-\text{age in years}) \times \text{body weight in kilograms}}{72 \times \text{serum creatinine (milligrams per 100 mL)}}
\]
Dosage of Dofetilide Adjusted for Creatinine Clearance

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Initial Dose (μg BID)</th>
<th>Adjustment for Δ QTc (μg/day)</th>
</tr>
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<tbody>
<tr>
<td>&gt;60</td>
<td>500</td>
<td>250</td>
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<tr>
<td>40–60</td>
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<tr>
<td>20–30</td>
<td>125</td>
<td>125</td>
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<tr>
<td>&lt;20</td>
<td>Not recommended</td>
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clearance (male) × 0.85) of Cockcroft and Gault to adjust dosage, and the 750 mg BID dose level was eliminated. Subsequent to these modifications, a substantial reduction in the incidence of torsade de pointes was noted. In DIAMOND-CHF, the incidence of torsade de pointes decreased from 7 of 146 (4.8%) to 18 of 616 (2.9%) after the protocol was amended. In all studies, treatment was initiated during in-hospital monitoring until presumed steady state had been addressed. QT intervals were measured before each dose, and a downward dose adjustment was permitted. Overall, torsade de pointes, defined in these studies as >10 beats of polymorphic ventricular tachycardia with a twisting QRS axis and long QT interval, was seen in 25 of 762 (3.3%) DIAMOND-CHF patients, 7 of 749 (0.9%) DIAMOND-MI patients, 12 of 1377 (0.9%) patients in supraventricular arrhythmia trials, and 11 of 443 (2.5%) patients in ventricular tachycardia trials. Most but not all documented episodes of torsade de pointes occurred during in-hospital therapy initiation and therefore excess fatalities were rare. Risk factors for torsade de pointes included higher dose, female sex, baseline QT > 450 ms, greater QTc increase during loading, and history of a sustained ventricular tachycardia. It is important to note that patients with QTc > 460 ms, resting heart rates < 50 bpm, or a history of polymorphic ventricular tachycardia were excluded from these trials.

The initial dosage of dofetilide should be based on the patient’s creatinine clearance (Table). Initial dosage should be conducted during in-hospital ECG monitoring, and the QTc should be checked 2 to 3 hours after each dose. If the change in QTc is ≥ 15% or if the QTc is > 500 ms, reduction in dose is recommended. At least 3 days of monitoring is required for this protocol.

Summary

Dofetilide is a new class III antiarrhythmic drug that produces both its antiarrhythmic and toxic effects through blockade of \( I_{\text{Kr}} \). Dofetilide has been shown to be effective for conversion of persistent atrial fibrillation and for maintenance of sinus rhythm after pharmacological and electrical cardioversion. Dofetilide has a narrow therapeutic range. Dosage should be adjusted on the basis of renal function and its pharmacological effect on the QT interval. A role for dofetilide has not yet been demonstrated for primary prevention of sudden death in patients with heart failure or after myocardial infarction or among those with a history of sustained ventricular tachycardia or fibrillation. Appropriate use of dofetilide by clinicians will require careful attention to renal function and the potential for drug interactions. In-hospital monitoring during therapy initiation is recommended to reduce the possibility of potentially fatal proarrhythmia.

References


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Dofetilide
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