

Key Characteristics of Greek Moderate Coffee Drinkers

	Coffee Consumption	
	1-2 cups/day	Rarely or never
Prevalence of diabetes	22%	34%
Prevalence of dyslipidemia	41%	55%
Prevalence of diagnosed cardiovascular disease	19%	26%
Mean BMI (kg/m ²)	28	29
Creatinine clearance (mL/min per 1.73 m ²)	70	65

Notes: Data from a study of 465 Ikaria residents aged 65-100 years on current treatment for hypertension. All differences are statistically significant.
Source: Dr. Chrysohoou

Greek-Style Coffee May Aid Arterial Elasticity

BY BRUCE JANCIN

FROM THE ANNUAL CONGRESS OF THE EUROPEAN SOCIETY OF CARDIOLOGY

STOCKHOLM – The fountain of youth just might be a basin filled with rich, strong coffee, a study of one of the world's longest-lived people has shown. "Our results suggest that drinking coffee

in moderation should be encouraged even in elderly hypertensive subjects, as it seems it may improve arterial aging. Maybe regular coffee consumption is one of the key elements of the longevity we have noticed in the Ikaria Islanders, Dr. Christina Chrysohoou said at the congress.

The Aegean Sea island of Ikaria has one of the world's highest proportions of

TIKOSYN® (dofetilide) Capsules

To minimize the risk of induced arrhythmia, patients initiated or re-initiated on TIKOSYN should be placed for a minimum of 3 days in a facility that can provide calculations of creatinine clearance, continuous electrocardiographic monitoring, and cardiac resuscitation. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment initiation education.

Brief Summary of Prescribing Information

INDICATIONS AND USAGE

Maintenance of Normal Sinus Rhythm (Delay in AF/AFI Recurrence)

TIKOSYN is indicated for the maintenance of normal sinus rhythm (delay in time to recurrence of atrial fibrillation/atrial flutter [AF/AFI]) in patients with atrial fibrillation/atrial flutter of greater than one week duration who have been converted to normal sinus rhythm. Because TIKOSYN can cause life threatening ventricular arrhythmias, it should be reserved for patients in whom atrial fibrillation/atrial flutter is highly symptomatic.

In general, antiarrhythmic therapy for atrial fibrillation/atrial flutter aims to prolong the time in normal sinus rhythm. Recurrence is expected in some patients.

Conversion of Atrial Fibrillation/Flutter

TIKOSYN is indicated for the conversion of atrial fibrillation and atrial flutter to normal sinus rhythm.

TIKOSYN has not been shown to be effective in patients with paroxysmal atrial fibrillation.

CONTRAINDICATIONS

TIKOSYN is contraindicated in patients with congenital or acquired long QT syndromes. TIKOSYN should not be used in patients with a baseline QT interval or QTc >440 msec (500 msec in patients with ventricular conduction abnormalities). TIKOSYN is also contraindicated in patients with severe renal impairment (calculated creatinine clearance <20 mL/min).

The concomitant use of verapamil or the cation transport system inhibitors cimetidine, trimethoprim (alone or in combination with sulfamethoxazole) or ketoconazole with TIKOSYN is contraindicated, as each of these drugs cause a substantial increase in dofetilide plasma concentrations. In addition, other known inhibitors of the renal cation transport system such as prochlorperazine and megestrol should not be used in patients on TIKOSYN.

The concomitant use of hydrochlorothiazide (alone or in combinations such as with triamterene) with TIKOSYN is contraindicated because this has been shown to significantly increase dofetilide plasma concentrations and QT interval prolongation.

TIKOSYN is also contraindicated in patients with a known hypersensitivity to the drug.

WARNINGS

Ventricular Arrhythmia: TIKOSYN (dofetilide) can cause serious ventricular arrhythmias, primarily torsade de pointes (TdP) type ventricular tachycardia, a polymorphic ventricular tachycardia associated with QT interval prolongation. QT interval prolongation is directly related to dofetilide plasma concentration. Factors such as reduced creatinine clearance or certain dofetilide drug interactions will increase dofetilide plasma concentration. The risk of TdP can be reduced by controlling the plasma concentration through adjustment of the initial dofetilide dose according to creatinine clearance and by monitoring the ECG for excessive increases in the QT interval.

Treatment with dofetilide must therefore be started only in patients placed for a minimum of three days in a facility that can provide electrocardiographic monitoring and in the presence of personnel trained in the management of serious ventricular arrhythmias. Calculation of the creatinine clearance for all patients must precede administration of the first dose of dofetilide.

The risk of dofetilide induced ventricular arrhythmia was assessed in three ways in clinical studies: 1) by description of the QT interval and its relation to the dose and plasma concentration of dofetilide; 2) by observing the frequency of TdP in TIKOSYN treated patients according to dose; 3) by observing the overall mortality rate in patients with atrial fibrillation and in patients with structural heart disease.

Relation of QT Interval to Dose: The QT interval increases linearly with increasing TIKOSYN dose.

Frequency of Torsade de Pointes: In the supraventricular arrhythmia population (patients with AF and other supraventricular arrhythmias) the overall incidence of torsade de pointes was 0.8%. The frequency of TdP by dose is shown in Table 4. There were no cases of TdP on placebo.

Table 4: Summary of Torsade de Pointes in Patients Randomized to Dofetilide by Dose; Patients with Supraventricular Arrhythmias

	TIKOSYN Dose				All Doses
	<250 mcg BID	250 mcg BID	>250-500 mcg BID	>500 mcg BID	
Number of Patients	217	388	703	38	1346
Torsade de Pointes	0	1 (0.3%)	6 (0.9%)	4 (10.5%)	11 (0.8%)

As shown in Table 5, the rate of TdP was reduced when patients were dosed according to their renal function.

Table 5: Incidence of Torsade de Pointes Before and After Introduction of Dosing According to Renal Function

Population:	Total	Before	After
	n/N %	n/N %	n/N %
Supraventricular Arrhythmias	11/1346 (0.8%)	6/193 (3.1%)	5/1153 (0.4%)
DIAMOND CHF	25/762 (3.3%)	7/148 (4.7%)	18/614 (2.9%)
DIAMOND MI	7/749 (0.9%)	3/101 (3.0%)	4/648 (0.6%)
DIAMOND AF	4/249 (1.6%)	0/43 (0%)	4/206 (1.9%)

The majority of the episodes of TdP occurred within the first three days of TIKOSYN therapy (10/11 events in the studies of patients with supraventricular arrhythmias; 19/25 and 4/7 events in DIAMOND CHF and DIAMOND MI, respectively; 2/4 events in the DIAMOND AF subpopulation).

Mortality: In a pooled survival analysis of patients in the supraventricular arrhythmia population (low prevalence of structural heart disease), deaths occurred in 0.9% (12/1346) of patients receiving TIKOSYN and 0.4% (3/677) in the placebo group. Adjusted for duration of therapy, primary diagnosis, age, gender, and prevalence of structural heart disease, the point estimate of the hazard ratio for the pooled studies (TIKOSYN/placebo) was 1.1 (95% CI: 0.3, 4.3). The DIAMOND CHF and MI trials examined mortality in patients with structural heart disease (ejection fraction ≤ 35%). In these large, double-blind studies, deaths occurred in 36% (541/1511) of TIKOSYN patients and 37% (560/1517) of placebo patients. In an analysis of 506 DIAMOND patients with atrial fibrillation/flutter at baseline, one year mortality on TIKOSYN was 31% vs. 32% on placebo.

Because of the small number of events, an excess mortality due to TIKOSYN cannot be ruled out with confidence in the pooled survival analysis of placebo-controlled trials in patients with supraventricular arrhythmias. However, it is reassuring that in two large placebo-controlled mortality studies in patients with significant heart disease (DIAMOND CHF/MI), there were no more deaths in TIKOSYN-treated patients than in patients given placebo.

Drug-Drug Interactions

Because there is a linear relationship between dofetilide plasma concentration and QTc, concomitant drugs that interfere with the metabolism or renal elimination of dofetilide may increase the risk of arrhythmia (torsade de pointes). TIKOSYN is metabolized to a small degree by the CYP3A4 isoenzyme of the cytochrome P450 system and an inhibitor of this system could increase systemic dofetilide exposure. More important, dofetilide is eliminated by cationic renal secretion, and three inhibitors of this process have been shown to increase systemic dofetilide exposure. The magnitude of the effect on renal elimination by cimetidine, trimethoprim and ketoconazole (all contraindicated concomitant uses with dofetilide) suggests that all renal cation transport inhibitors should be contraindicated.

Hypokalemia and Potassium-Depleting Diuretics

Hypokalemia or hypomagnesemia may occur with administration of potassium-depleting diuretics, increasing the potential for torsade de pointes. Potassium levels should be within the normal range prior to administration of TIKOSYN and maintained in the normal range during administration of TIKOSYN.

Use with Drugs that Prolong QT Interval and Antiarrhythmic Agents

The use of TIKOSYN in conjunction with other drugs that prolong the QT interval has not been studied and is not recommended. Such drugs include phenothiazines, cisapride, bepridil, tricyclic antidepressants, certain oral macrolides, and certain fluoroquinolones.

Class I or Class III antiarrhythmic agents should be withheld for at least three half-lives prior to dosing with TIKOSYN. In clinical trials, TIKOSYN was administered to patients previously treated with oral amiodarone only if serum amiodarone levels were below 0.3 mg/L or amiodarone had been withdrawn for at least three months.

PRECAUTIONS

Renal Impairment

The overall systemic clearance of dofetilide is decreased and plasma concentration increased with decreasing creatinine clearance. The dose of TIKOSYN must be adjusted based on creatinine clearance. Patients undergoing dialysis were not included in clinical studies, and appropriate dosing recommendations for these patients are unknown. There is no information about the effectiveness of hemodialysis in removing dofetilide from plasma.

Hepatic Impairment

After adjustment for creatinine clearance, no additional dose adjustment is required for patients with mild or moderate hepatic impairment. Patients with severe hepatic impairment have not been studied. TIKOSYN should be used with particular caution in these patients.

Cardiac Conduction Disturbances

Animal and human studies have not shown any adverse effects of dofetilide on conduction velocity. No effect on AV nodal conduction following TIKOSYN treatment was noted in normal volunteers and in patients with 1st degree heart block. Patients with sick sinus syndrome or with 2nd or 3rd degree heart block were not included in the Phase 3 clinical trials unless a functioning pacemaker was present. TIKOSYN has been used safely in conjunction with pacemakers (53 patients in DIAMOND studies, 136 in trials in patients with ventricular and supraventricular arrhythmias).

Information for Patients

Please refer patient to the patient package insert.

Prior to initiation of TIKOSYN therapy, the patient should be advised to read the patient package insert and reread it each time therapy is renewed in case the patient's status has changed. The patient should be fully instructed on the need for compliance with the recommended dosing of TIKOSYN and the potential for drug interactions, and the need for periodic monitoring of QTc and renal function to minimize the risk of serious abnormal rhythms.

Medications and Supplements: Assessment of patients' medication history should include all over-the-counter, prescription and herbal/natural preparations with emphasis on preparations that may affect the pharmacokinetics of TIKOSYN such as cimetidine, trimethoprim alone or in combination with sulfamethoxazole, prochlorperazine, megestrol, ketoconazole, hydrochlorothiazide (alone or in combinations such as with triamterene), other cardiovascular drugs, phenothiazines, and tricyclic antidepressants. If a patient is taking TIKOSYN and requires anti-ulcer therapy, omeprazole, ranitidine or antacids (aluminum and magnesium hydroxides) should be used as alternatives to cimetidine, as these agents have no effect on the pharmacokinetics of TIKOSYN. Patients should be instructed to notify their health care providers of any change in over-the-counter, prescription or supplement use. If a patient is hospitalized or is prescribed a new medication for any condition, the patient must inform the health care provider of ongoing TIKOSYN therapy. Patients should also check with their health care provider and/or pharmacist prior to taking a new over-the-counter preparation.

Electrolyte Imbalance: If patients experience symptoms that may be associated with altered electrolyte balance, such as excessive or prolonged diarrhea, sweating, or vomiting or loss of appetite or thirst, these conditions should immediately be reported to their health care provider.

Dosing Schedule: Patients should be instructed NOT to double the next dose if a dose is missed. The next dose should be taken at the usual time.

Drug/Laboratory Test Interactions

None known.

Drug-Drug Interactions

Cimetidine: Concomitant use of cimetidine is contraindicated. Cimetidine at 400 mg BID (the usual prescription dose) co-administered with TIKOSYN (500 mcg BID) for 7 days has been shown to increase dofetilide plasma levels by 58%. Cimetidine at doses of 100 mg BID (OTC dose) resulted in a 13% increase in dofetilide plasma levels (500 mcg single dose). No studies have been conducted at intermediate doses of cimetidine. If a patient requires TIKOSYN and anti-ulcer therapy, it is suggested that omeprazole, ranitidine, or antacids (aluminum and magnesium hydroxides) be used as alternatives to cimetidine, as these agents have no effect on the pharmacokinetic profile of TIKOSYN.

Verapamil: Concomitant use of verapamil is contraindicated. Co-administration of TIKOSYN with verapamil resulted in increases in dofetilide peak plasma levels of 42%, although overall exposure to dofetilide was not significantly increased. In an analysis of the supraventricular arrhythmia and DIAMOND patient populations, the concomitant administration of verapamil with dofetilide was associated with a higher occurrence of torsade de pointes.

Ketoconazole: Concomitant use of ketoconazole is contraindicated. Ketoconazole at 400 mg daily (the maximum approved prescription dose) co-administered with TIKOSYN (500 mcg BID) for 7 days has been shown to increase dofetilide C_{max} by 53% in males and 97% in females, and AUC by 41% in males and 69% in females.

Trimethoprim Alone or in Combination with Sulfamethoxazole: Concomitant use of trimethoprim alone or in combination with sulfamethoxazole is contraindicated. Trimethoprim 160 mg in combination with 800 mg sulfamethoxazole co-administered BID with TIKOSYN (500 mcg BID) for 4 days has been shown to increase dofetilide AUC by 103% and C_{max} by 93%.

Hydrochlorothiazide (HCTZ) Alone or in Combination with Triamterene: Concomitant use of HCTZ alone or in combination with triamterene is contraindicated. HCTZ 50 mg QD or HCTZ/triamterene 50/100 mg QD was co-administered with TIKOSYN (500 mcg BID) for 5 days (following 2 days of diuretic use at half dose). In patients receiving HCTZ alone, dofetilide AUC increased by 27% and C_{max} by 21%. However, the pharmacodynamic effect increased by 197% (QTc increase over time) and by 95% (maximum QTc increase). In patients receiving HCTZ in combination with triamterene, dofetilide AUC increased by 30% and C_{max} by 16%. However, the pharmacodynamic effect increased by 190% (QTc increase over time) and by 84% (Maximum QTc increase). The pharmacodynamic effects can be explained by a combination of the increase in dofetilide exposure and the reductions in serum potassium. In the DIAMOND trials, 1252 patients were treated with TIKOSYN and diuretics concomitantly of whom 493 died compared to 508 deaths among the 1248 patients receiving placebo and diuretics. Of the 229 patients who had potassium depleting diuretics added to their concomitant medications in the DIAMOND trials, the patients on TIKOSYN had a non-significantly reduced relative risk for death of 0.68 (95% CI 0.376, 1.230).

Potential Drug Interactions

Dofetilide is eliminated in the kidney by cationic secretion. Inhibitors of renal cationic secretion are contraindicated with TIKOSYN. In addition, drugs that are actively secreted via this route (e.g., triamterene, mefloquine and amiloride) should be co-administered with care as they might increase dofetilide levels.

Dofetilide is metabolized to a small extent by the CYP3A4 isoenzyme of the cytochrome P450 system. Inhibitors of the CYP3A4 isoenzyme could increase systemic dofetilide exposure. Inhibitors of this isoenzyme (e.g., macrolide antibiotics, azole antifungal agents, protease inhibitors, serotonin reuptake inhibitors, amiodarone, cannabidiol, diltiazem, grapefruit juice, nefazodone, norfloxacin, quinidine, zafirlucast) should be cautiously coadministered with TIKOSYN as they can potentially increase dofetilide levels. Dofetilide is not an inhibitor of CYP3A4 nor of other cytochrome P450 isoenzymes (e.g., CYP2C9, CYP2D6) and is not expected to increase levels of drugs metabolized by CYP3A4.

Other Drug Interaction Information

Digoxin: Studies in healthy volunteers have shown that TIKOSYN does not affect the pharmacokinetics of digoxin. In patients, the concomitant administration of digoxin with dofetilide was associated with a higher occurrence of torsade de pointes. It is not clear whether this represents an interaction with TIKOSYN or the presence of more severe structural heart disease in patients on digoxin; structural heart disease is a known risk factor for arrhythmia. No increase in mortality was observed in patients taking digoxin as concomitant medication.

Other Drugs: In healthy volunteers, amlodipine, phenytoin, glyburide, ranitidine, omeprazole, hormone replacement therapy (a combination of conjugated estrogens and medroxyprogesterone), antacid (aluminum and magnesium hydroxides) and theophylline did not affect the pharmacokinetics of TIKOSYN. In addition, studies in healthy volunteers have shown that TIKOSYN does not affect the pharmacokinetics or pharmacodynamics of warfarin, or the pharmacokinetics of propranolol (40 mg twice daily), phenytoin, theophylline, or oral contraceptives.

Population pharmacokinetic analyses were conducted on plasma concentration data from 1445 patients in clinical trials to examine the effects of concomitant medications on clearance or volume of distribution of dofetilide. Concomitant medications were grouped as ACE inhibitors, oral anticoagulants, calcium channel blockers, beta blockers, cardiac glycosides, inducers of CYP3A4, substrates and inhibitors of CYP3A4, substrates and inhibitors of P-glycoprotein, nitrates, sulphonylureas, loop diuretics, potassium sparing diuretics, thiazide diuretics, substrates and inhibitors of tubular organic cation transport, and QTc-prolonging drugs. Differences in

individuals who survive into their 90s and 100s. Residents of the isolated Greek island were featured in "The Blue Zones: Lessons for Living Longer From the People Who've Lived the Longest," by Dan Buettner (National Geographic Books, 2008).

Seeking an explanation for the Ikarians' exceptional longevity, last year Dr. Chrysohoou led a 5-month University of Athens-sponsored in-depth study of 343 male and 330 female longtime residents aged 65-100 years. As a cardiologist, Dr. Chrysohoou said, one of the factors she was particularly eager to examine was

coffee consumption, since it is a deeply embedded part of the Ikarian way of life, and also because coffee – especially Greek-coffee – is a rich source of antioxidants and anti-inflammatory compounds, which could have a salutary effect on cardiovascular risk.

This indeed appeared to be the case. Among the 465 study participants being treated for hypertension, those who were moderate coffee drinkers – averaging 1-2 of the traditional small 50-mL cups daily – had a significantly lower prevalence of diabetes, dyslipidemia, and cardiovascular disease as well as a lower

mean body mass index and higher creatinine clearance than did hypertensive non-coffee drinkers (see box, p. 16).

Of particular interest was the finding that hypertensive moderate coffee drinkers had significantly greater aortic distensibility, as measured echocardiographically, than did hypertensive subjects who consumed coffee rarely or never.

Consumption of 1-2 cups/day remained an independent predictor of enhanced arterial elasticity after adjustment for potential confounders including age, physical activity, body mass in-

dex, blood pressure, education, diabetes, smoking, and diet.

Islanders who drank less than 1 cup or at least 3 cups of coffee per day did not derive any benefit in terms of aortic distensibility compared with coffee teetotalers. This is probably because modest quaffers do not obtain adequate quantities of the beneficial polyphenolic compounds and other micronutrients, while people who consume 3 or more cups daily ingest so much caffeine that the pressor response outweighs the positive effects of the micronutrients, according to Dr. Chrysohoou.

Traditional Greek coffee is very strong and dark. It is made by boiling the beans for 2-3 minutes. The resultant beverage contains up to 50 times greater concentrations of cafestol, kahweol, and other



'Drinking coffee in moderation should be encouraged, even in elderly hypertensive subjects.'

DR. CHRYSOHOOU

diterpenes than those of filtered coffee. Greek coffee also is rich in flavonoids, niacin, magnesium, potassium, and vitamin E, she explained.

One caveat regarding the study findings is that coffee drinking on Ikaria is very much a social experience. The elderly study participants generally take their coffee while socializing in the morning or early afternoon with longtime friends in tavernas and cafes, or with family at home. Coffee consumption on the island is a relaxing, unhurried experience enjoyed while discussing daily events.

"The psychological and social circumstances play an important role," she said.

"I'm a clinical cardiologist, and most clinicians forbid coffee for their hypertensive patients," noted Dr. Xavier Bosch of the University of Barcelona, who added he will reconsider his stance as a result of the Greek study.

The other key factor Dr. Chrysohoou and her coworkers identified as likely to contribute to the extended life expectancy of Ikaria Islanders is that these oldest residents are of a generation that tends to adhere most strictly to the traditional Mediterranean diet as popularized by the late University of Minnesota cardiovascular epidemiologist Ancel Keys.

Dr. Chrysohoou declared having no financial conflicts.



Consumption of 1-2 cups/day was a predictor of enhanced arterial elasticity.

clearance between patients on these medications (at any occasion in the study) and those off medications varied between -16% and +3%. The mean clearances of dofetilide were 16% and 15% lower in patients on thiazide diuretics and inhibitors of tubular organic cation transport, respectively.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Dofetilide had no genotoxic effects, with or without metabolic activation, based on the bacterial mutation assay and tests of cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes. Rats and mice treated with dofetilide in the diet for two years showed no evidence of an increased incidence of tumors compared to controls. The highest dofetilide dose administered for 24 months was 10 mg/kg/day to rats and 20 mg/kg/day to mice. Mean dofetilide AUCs_{0-24h} at these doses were about 26 and 10 times, respectively, the maximum likely human AUC.

There was no effect on mating or fertility when dofetilide was administered to male and female rats at doses as high as 1.0 mg/kg/day, a dose that would be expected to provide a mean dofetilide AUC_{0-24h} about 3 times the maximum likely human AUC. Increased incidences of testicular atrophy and epididymal oligospermia and a reduction in testicular weight were, however, observed in other studies in either species at doses below 2 mg/kg/day. The clearest drug-effect associations were for sternal and vertebral anomalies in both species; cleft palate, adactyly, levocardia, dilation of cerebral ventricles, hydroureter, hydronephroses, and unossified metacarpal in the rat; and increased incidence of unossified calcaneum in the mouse. The "no observed adverse effect dose" in both species was 0.5 mg/kg/day. The mean dofetilide AUCs_{0-24h} at this dose in the rat and mouse are estimated to be about equal to the maximum likely human AUC and about half the likely human AUC, respectively. There are no adequate and well controlled studies in pregnant women. Therefore, dofetilide should only be administered to pregnant women where the benefit to the patient justifies the potential risk to the fetus.

Pregnancy Category C

Dofetilide has been shown to adversely affect *in utero* growth and survival of rats and mice when orally administered during organogenesis at doses of 2 or more mg/kg/day. Other than an increased incidence of non-ossified 5th metacarpal, and the occurrence of hydroureter and hydronephroses at doses as low as 1 mg/kg/day in the rat, structural anomalies associated with drug treatment were not observed in either species at doses below 2 mg/kg/day. The clearest drug-effect associations were for sternal and vertebral anomalies in both species; cleft palate, adactyly, levocardia, dilation of cerebral ventricles, hydroureter, hydronephroses, and unossified metacarpal in the rat; and increased incidence of unossified calcaneum in the mouse. The "no observed adverse effect dose" in both species was 0.5 mg/kg/day. The mean dofetilide AUCs_{0-24h} at this dose in the rat and mouse are estimated to be about equal to the maximum likely human AUC and about half the likely human AUC, respectively. There are no adequate and well controlled studies in pregnant women. Therefore, dofetilide should only be administered to pregnant women where the benefit to the patient justifies the potential risk to the fetus.

Nursing Mothers

There is no information on the presence of dofetilide in breast milk. Patients should be advised not to breast feed an infant if they are taking TIKOSYN.

Geriatric Use

Of the total number of patients in clinical studies of TIKOSYN, 46% were 65 to 89 years old. No overall differences in safety, effect on QTc, or effectiveness were observed between elderly and younger patients. Because elderly patients are more likely to have decreased renal function with a reduced creatinine clearance, care must be taken in dose selection.

Use in Women

Female patients constituted 32% of the patients in the placebo-controlled trials of TIKOSYN. As with other drugs that cause torsade de pointes, TIKOSYN was associated with a greater risk of torsade de pointes in female patients than in male patients. During the TIKOSYN clinical development program the risk of torsade de pointes in females was approximately 3 times the risk in males. Unlike torsade de pointes, the incidence of other ventricular arrhythmias was similar in female patients receiving TIKOSYN and patients receiving placebo. Although no study specifically investigated this risk, in post-hoc analyses, no increased mortality was observed in females on TIKOSYN compared to females on placebo.

Pediatric Use

The safety and effectiveness of TIKOSYN in children (<18 years old) has not been established.

ADVERSE REACTIONS

The TIKOSYN clinical program involved approximately 8,600 patients in 130 clinical studies of normal volunteers and patients with supraventricular and ventricular arrhythmias. TIKOSYN was administered to 5,194 patients, including two large, placebo-controlled mortality trials (DIAMOND CHF and DIAMOND MI) in which 1,511 patients received TIKOSYN for up to three years.

In the following section, adverse reaction data for cardiac arrhythmias and non-cardiac adverse reactions are presented separately for patients included in the supraventricular arrhythmia development program and for patients included in the DIAMOND CHF and MI mortality trials.

In studies of patients with supraventricular arrhythmias a total of 1346 and 677 patients were exposed to TIKOSYN and placebo for 551 and 207 patient years, respectively. A total of 8.7% of patients in the dofetilide groups were discontinued from clinical trials due to adverse events compared to 8.0% in the placebo groups. The most frequent reason for discontinuation (>1%) was ventricular tachycardia (2.0% on dofetilide vs. 1.3% on placebo). The most frequent adverse events were headache, chest pain, and dizziness.

Serious Arrhythmias and Conduction Disturbances: Torsade de pointes is the only arrhythmia that showed a dose-response relationship to TIKOSYN treatment. It did not occur in placebo treated patients. The incidence of torsade de pointes in patients with supraventricular arrhythmias was 0.8% (11/1346). The incidence of torsade de pointes in patients who were dosed according to the recommended dosing regimen was 0.8% (4/525). Table 6 shows the frequency by randomized dose of serious arrhythmias and conduction disturbances reported as adverse events in patients with supraventricular arrhythmias.

Table 6: Incidence of Serious Arrhythmias and Conduction Disturbances in Patients with Supraventricular Arrhythmias

Arrhythmia event:	TIKOSYN Dose				Placebo N=677
	<250 mcg BID N=217	250 mcg BID N=388	>250-500 mcg BID N=703	>500 mcg BID N=38	
Ventricular arrhythmias* ^	3.7%	2.6%	3.4%	15.8%	2.7%
Ventricular fibrillation	0	0.3%	0.4%	2.6%	0.1%
Ventricular tachycardia^	3.7%	2.6%	3.3%	13.2%	2.5%
Torsade de pointes	0	0.3%	0.9%	10.5%	0
Various forms of block					
AV block	0.9%	1.5%	0.4%	0	0.3%
Bundle branch block	0	0.5%	0.1%	0	0.1%
Heart block	0	0.5%	0.1%	0	0.1%

* Patients with more than one arrhythmia are counted only once in this category.
^ Ventricular arrhythmias and ventricular tachycardia include all cases of torsade de pointes.

In the DIAMOND trials a total of 1511 patients were exposed to TIKOSYN for 1757 patient years. The incidence of torsade de pointes was 3.3% in CHF patients and 0.9% in patients with a recent MI.

Table 7 shows the incidence of serious arrhythmias and conduction disturbances reported as adverse events in the DIAMOND subpopulation that had AF at entry to these trials.

Table 7: Incidence of Serious Arrhythmias and Conduction Disturbances in Patients with AF at Entry to the DIAMOND Studies

	TIKOSYN N=249	Placebo N=257
Ventricular arrhythmias* ^	14.5%	13.6%
Ventricular fibrillation	4.8%	3.1%
Ventricular tachycardia^	12.4%	11.3%
Torsade de pointes	1.6%	0
Various forms of block		
AV block	0.8%	2.7%
(Left) bundle branch block	0	0.4%
Heart block	1.2%	0.8%

* Patients with more than one arrhythmia are counted only once in this category.
^ Ventricular arrhythmias and ventricular tachycardia include all cases of torsade de pointes.

Other Adverse Reactions: Table 8 presents other adverse events reported with a frequency of >2% on TIKOSYN and reported numerically more frequently on TIKOSYN than on placebo in the studies of patients with supraventricular arrhythmias.

Table 8: Frequency of Adverse Events Occurring at >2% on TIKOSYN, and Numerically More Frequently on TIKOSYN than Placebo in Patients with Supraventricular Arrhythmias

Adverse Event	TIKOSYN %	Placebo %
headache	11	9
chest pain	10	7
dizziness	8	6
respiratory tract infection	7	5
dyspnea	6	5
nausea	5	4
flu syndrome	4	2
insomnia	4	3
accidental injury	3	1
back pain	3	2
procedure (medical/surgical/health service)	3	2
diarrhea	3	2
rash	3	2
abdominal pain	3	2

Adverse events reported at a rate >2% but no more frequently on TIKOSYN than on placebo were: angina pectoris, anxiety, arthralgia, asthenia, atrial fibrillation, complications (application, injection, incision, insertion, or device), hypertension, pain, palpitation, peripheral edema, supraventricular tachycardia, sweating, urinary tract infection, ventricular tachycardia.

The following adverse events have been reported with a frequency of ≤ 2% and numerically more frequently with TIKOSYN than placebo in patients with supraventricular arrhythmias: angioedema, bradycardia, cerebral ischemia, cerebrovascular accident, edema, facial paralysis, flaccid paralysis, heart arrest, increased cough, liver damage, migraine, myocardial infarct, paralysis, paresthesia, sudden death, and syncope.

The incidences of clinically significant laboratory test abnormalities in patients with supraventricular arrhythmias were similar for patients on TIKOSYN and those on placebo. No clinically relevant effects were noted in serum alkaline phosphatase, serum GGT, LDH, AST, ALT, total bilirubin, total protein, blood urea nitrogen, creatinine, serum electrolytes (calcium, chloride, glucose, magnesium, potassium, sodium) or creatine kinase. Similarly, no clinically relevant effects were observed in hematologic parameters.

In the DIAMOND population, adverse events other than those related to the post-infarction and heart failure patient population were generally similar to those seen in the supraventricular arrhythmia groups.

OVERDOSAGE

There is no known antidote to TIKOSYN; treatment of overdose should therefore be symptomatic and supportive. The most prominent manifestation of overdose is likely to be excessive prolongation of the QT interval.

In cases of overdose cardiac monitoring should be initiated. Charcoal slurry may be given soon after overdosing but has been useful only when given within 15 minutes of TIKOSYN administration. Treatment of torsade de pointes or overdose may include administration of isoproterenol infusion, with or without cardiac pacing. Administration of intravenous magnesium sulfate may be effective in the management of torsade de pointes. Close medical monitoring and supervision should continue until the QT interval returns to normal levels.

Isoproterenol infusion into anesthetized dogs with cardiac pacing rapidly attenuates the dofetilide-induced prolongation of atrial and ventricular effective refractory periods in a dose-dependent manner. Magnesium sulfate, administered prophylactically either intravenously or orally in a dog model, was effective in the prevention of dofetilide-induced torsade de pointes ventricular tachycardia. Similarly, in man, intravenous magnesium sulfate may terminate torsade de pointes, irrespective of cause.

TIKOSYN overdose was rare in clinical studies; there were two reported cases of TIKOSYN overdose in the oral clinical program. One patient received very high multiples of the recommended dose (28 capsules), was treated with gastric aspiration 30 minutes later, and experienced no events. One patient inadvertently received two 500 mcg doses one hour apart and experienced ventricular fibrillation and cardiac arrest 2 hours after the second dose.

In the supraventricular arrhythmia population only 38 patients received doses greater than 500 mcg BID, all of whom received 750 mcg BID irrespective of creatinine clearance. In this very small patient population the incidence of torsade de pointes was 10.5% (4/38 patients), and the incidence of new ventricular fibrillation was 2.6% (1/38 patients).