

IMPLEMENTING HEALTH REFORM

The Prevention and Public Health Fund

One of the controversial elements of the Affordable Care Act is creation of the Prevention and Public Health Fund, which sets aside about \$15 billion to finance public health programs over the next decade. Under the program, the Health and Human Services department awards grants for projects that prevent illness or promote health. For example, since 2010, HHS has

awarded more than \$42 million to organizations in California for a variety of programs including training more primary care residents, building laboratory capacity, and reducing tobacco use. Supporters of the program say that it is an important investment in prevention that will ultimately save money by detecting diseases early and better managing costly chronic conditions. Opponents

have deemed it a “slush fund” and are seeking to eliminate it. In April, the House approved legislation that would dismantle the Fund; however, the Senate has not taken action on the bill. The Prevention Fund could also be a target for cuts by the Joint Select Committee on Deficit Reduction, which is tasked with cutting \$1.5 trillion from the federal budget this fall.

Dr. Georges C. Benjamin, executive director of the American Public Health Association (APHA), offers his views on why the Prevention Fund is essential to public health and how it may fare in the current political environment.

CARDIOLOGY NEWS: Why do you think the Prevention Fund has been caught up in politics?

TIKOSYN® (dofetilide) Capsules

Brief Summary of Prescribing Information

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.

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 1. There were no cases of TdP on placebo.

Table 1: Summary of Torsade de Pointes in Patients Randomized to Dofetilide by Dose; Patients with Supraventricular Arrhythmias

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

As shown in Table 2, the rate of TdP was reduced when patients were dosed according to their renal function.

Table 2: 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 (4.7%)
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 Medication Guide.

Prior to initiation of TIKOSYN therapy, the patient should be advised to read the Medication Guide 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.

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.

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 rats. Reduced testicular weight and increased incidence of testicular atrophy were also consistent findings in dogs and mice. The no effect doses for these findings in chronic administration studies in these 3 species (3, 0.1 and 6 mg/kg/day) were associated with mean dofetilide AUCs that were about 4, 1.3 and 3 times the maximum likely human AUC, respectively.

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,

Dr. Benjamin: I think the Prevention Fund has been grossly misunderstood. For years, public health has been the most underinvested part of our health system. We’ve had “yo-yo” funding with a patchwork of funding streams. The goal of the Prevention Fund was to build on our existing funding sources and, for the first time, create a stable, reliable funding stream, which would allow the system to mature and reach its full potential. People who want to demonize the fund have said things that don’t represent its intent. The money is being used to build a sustainable public health system

and really begin to transform the health system, which I believe will dramatically improve the health and well-being of the people in our country.

CN: The APHA supported the Prevention Fund’s creation. Why is this type of investment important?

Dr. Benjamin: I spent most of my early years in emergency medicine, so I’ve seen



first-hand the effects of preventable disease. At APHA, we felt this was the best

The Fund's goal was to replace ‘yo-yo,’ patchwork funding with a stable, reliable funding stream for the first time.

DR. BENJAMIN

our health care costs. If we don’t do this now, it’s going to be years before we can

opportunity to tackle diseases that we should try to reduce from moral, ethical, and humanistic perspectives. But from a pure fiscal perspective, this is also our best chance to address some of

actually begin to get our hands around it. To have a major national restructuring of the way we deliver health care services, and not put in a prevention component would be foolhardy.

CN: Can prevention efforts like this really save money?

Dr. Benjamin: It depends. Just like in clinical care, there are things that save money and there are things that are expensive but have enormous value. And then there are some things that can either cost or save money depending on the situation. We know that screening for high blood pressure is cheap. We know that identifying early who has high blood sugar and high cholesterol is cheap. We believe that ultimately these people, whose conditions have been identified and controlled early, will live longer and healthier and save the system money. For instance, every patient with diabetes that does not progress to diabetic retinopathy represents as a huge savings for the health system. But what often doesn’t get captured in our economic analyses is the others savings outside of health care. For example, if a child doesn’t get exposed to lead because of a good public health program and they don’t suffer the complications from the lead exposure, there are savings to the health system but also savings to other sectors. In that case, we don’t count the savings from special-education programs. We don’t count the potential savings to the juvenile justice system. When folks say prevention doesn’t save money, they are usually looking only in the health bucket.

CN: Do you think the Prevention Fund is likely to survive in the long run?

Dr. Benjamin: Yes. The Prevention Fund will survive. We will make our case. If our nation is going to continue to throw \$2.5 trillion into health care, to spend only about 3% of that on prevention is poor public policy. I hope that we’ll be able to make the case that not only is this Fund needed, but that the amount of money dedicated to this area must grow.

DR. BENJAMIN is currently serving as a distinguished fellow in public health at Hunter College, part of the City University of New York system. He will return to his role as executive director of the American Public Health Association in 2012. Previously he served as the Secretary of the Maryland Department of Health and Mental Hygiene.

adactly, 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 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 3 shows the frequency by randomized dose of serious arrhythmias and conduction disturbances reported as adverse events in patients with supraventricular arrhythmias.

Table 3: Incidence of Serious Arrhythmias and Conduction Disturbances in Patients with Supraventricular Arrhythmias

Arrhythmia event:	TIKOSYN				Placebo
	<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 4 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 4: Incidence of Serious Arrhythmias and Conduction Disturbances in Patients with AF at Entry to the DIAMOND Studies

	TIKOSYN	Placebo
	N=249	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 5 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 5: 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.

Footnotes

*A total of 996 patients with a one week to two year history of atrial fibrillation/atrial flutter were enrolled. Both studies randomized patients to placebo or to doses of TIKOSYN 125 mcg, 250 mcg, 500 mcg, or in one study a comparator drug, given twice a day (these doses were lowered based on calculated creatinine clearance and, in one of the studies, for QT interval or QTc).

^The 2 DIAMOND studies (The Danish Investigations of Arrhythmia and Mortality on Dofetilide) were 3-year trials comparing the effects of TIKOSYN and placebo on mortality and morbidity in patients with impaired left ventricular (LV) function (ejection fraction ≤35%). One study was in patients with moderate to severe (60% NYHA Class III or IV) congestive heart failure (DIAMOND-CHF; N=1518), and the other was in patients with recent myocardial infarction (DIAMOND-MI; N=1510), of whom 40% had NYHA Class III or IV heart failure. Both groups were at relatively high risk of sudden death. The DIAMOND trials were intended to determine whether TIKOSYN could reduce that risk.

^Including ischemic heart disease, cardiomyopathies, and valvular disease.

References

1. Tikosyn [prescribing information]. New York, NY: Pfizer Inc; 2006.
2. Torp-Pedersen C, Møller M, Bloch-Thomsen PE, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. *N Engl J Med*. 1999;341(12):857-865.

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