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This section presents highlights of the contents of the TIKOSYN® (dofetilide) product monograph and refers you to more detailed information in the text.

**BOXED WARNING**

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.

For detailed instructions regarding dose selection, see DOSE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSE AND ADMINISTRATION.

**INDICATIONS**

- **Maintenance of Normal Sinus Rhythm (NSR)**
  TIKOSYN is indicated for the maintenance of NSR (delay in time to recurrence of atrial fibrillation/atrial flutter [AF/AFl]) in patients with AF/AFl of greater than one week duration who have been converted to NSR. Because TIKOSYN can cause life-threatening ventricular arrhythmias, it should be reserved for patients in whom AF/AFl is highly symptomatic. In general, antiarrhythmic therapy for AF/AFl aims to prolong the time in NSR. Recurrence is expected in some patients (see page 20).

- **Conversion of AF/AFl**
  TIKOSYN is indicated for the conversion of AF and AFl to NSR (see page 20).

- Tikosyn has not been shown to be effective in patients with paroxysmal AF (see page 20).

**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 contraindicated in patients with severe renal impairment (calculated creatinine clearance [\(\text{Cl}_{\text{cr}}\)] < 20 mL/min).

- The concomitant use of verapamil, the cation transport system inhibitors cimetidine, trimethoprim (alone or in combination with sulfamethoxazole), or ketoconazole with TIKOSYN is contraindicated (see PRECAUTIONS, Drug-Drug Interactions) as each of these drugs causes 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 (see PRECAUTIONS, Drug-Drug Interactions) because this has been shown to significantly increase dofetilide plasma concentrations and QT interval prolongation (see page 36).

- TIKOSYN is also contraindicated in patients with a known hypersensitivity to the drug (see page 36).
WARNINGS

- Ventricular Arrhythmia: TIKOSYN 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 CLcr 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 CLcr and by monitoring the electrocardiograph (ECG) for excessive increases in the QT interval (see page 36).

- 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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION (see page 68).

PHARMACOLOGY: MECHANISM OF ACTION AND ELECTROPHYSIOLOGIC EFFECTS

- TIKOSYN, a class III antiarrhythmic, produces blockade of Ik,(with no relevant blockade of other repolarizing potassium currents (eg, Ik1, Ik1) (see pages 12 and 13).

PHARMACOLOGY: HEMODYNAMIC EFFECTS

- TIKOSYN has no negative inotropic effects (see page 13).

- TIKOSYN has no effect on the following:
  - Cardiac output
  - Cardiac index
  - Stroke volume index
  - Systemic vascular resistance
  (see page 13)

In the overall clinical program, TIKOSYN did not affect blood pressure: heart rate was decreased by 4 to 6 beats per minute (see page 13).
PHARMACOKINETICS

- TIKOSYN has a terminal half-life ($t_{1/2}$) of approximately 10 hours, which permits twice-daily dosing (see page 15).

- Renal excretion of dofetilide accounts for approximately 80% of its elimination. Therefore, initial dosing must be adjusted based on the calculated $\text{Cl}_{\text{cr}}$ (see pages 15 and 38).

- TIKOSYN 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 (see page 38).

- The relationship between plasma levels of TIKOSYN and the change from baseline in QTc is predictable and linear (see pages 16 and 17).

CLINICAL EFFICACY

- The dosage of TIKOSYN must be individualized for the patient’s renal function and QTc response to therapy. This dosing strategy (dosing algorithm) was also used in the clinical trials. Thus, where results are presented by the dosage, this “dosage” was the starting value for the calculations in the algorithm. Each dosing group includes both patients who received the dosage shown as well as patients entered into the dosing algorithm for the dosage shown, but who received lower actual dosages because of the calculations in the algorithm.

- At the recommended 500 mcg BID dosage, TIKOSYN converted 30% of patients to NSR versus 1% conversion with placebo (see page 24).

- Of patients who converted pharmacologically, approximately 70% converted within 24 to 36 hours (see page 31).

- At 12 months, the probabilities of remaining in NSR were 58% for patients who received TIKOSYN 500 mcg BID compared with 25% for those given placebo ($P<.001$) (see page 34).

- The arrhythmia-free interval with TIKOSYN was > 365 days versus 34 days with placebo ($P<.001$) (see page 27).

- Efficacy results for TIKOSYN 250 mcg BID were the following: TIKOSYN converted 10% and 11% of patients to NSR versus 1% with placebo; at 12 months, the probabilities of remaining in NSR were 37% and 51% with TIKOSYN, compared with 25% and 21% with placebo; at 12 months, 26% and 42% of patients were still in NSR and on TIKOSYN, compared with 22% and 16% on placebo; the arrhythmia-free interval with TIKOSYN was 179 to > 365 days versus 34 days with placebo (see pages 24, 27, 31 and 34).
CLINICAL SAFETY

The safety of TIKOSYN was evaluated in 3 ways: by looking at the effect of TIKOSYN on mortality, the incidence of TdP in the supraventricular arrhythmia (SVA) population, and the rate of nuisance side effects (see page 50).

MORTALITY

The results of the 2 large-scale (N=3028) long-term (up to 3-year follow-up) mortality studies — Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) CHF (New York Heart Association [NYHA] class III-IV) and DIAMOND MI (median 3 days post-MI) — indicated that TIKOSYN produced no excess mortality or morbidity in patients with significant structural heart disease (SHD) when initiated in-hospital and administered according to renal function and QTc response to therapy. CLcr was calculated using a modified Cockcroft-Gault formula (see pages 37, 48, and 53-56).

A retrospective analysis of 506 patients with AF at baseline randomized to 250 mcg BID in the 2 DIAMOND trials indicated that treatment with TIKOSYN did not adversely affect mortality in patients with left ventricular (LV) dysfunction and AF when the dose of TIKOSYN was adjusted for renal function and QTc response to therapy (see pages 57-59).

TD P

In the SVA population (patients with AF and other SVAs evaluated in 10 double-blind, placebo-controlled clinical trials), the overall incidence of TdP for all doses was 0.8%. At the recommended 500 mcg BID TIKOSYN dose, the frequency of TdP was 0.9% (6 of 703 patients) when dose was adjusted for renal function and QT response. As noted above, the rate of TdP was reduced when patients were dosed according to their renal function (see page 37).

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

Please see full prescribing information and patient information for TIKOSYN® (dofetilide) capsules in back cover pocket.
MOST COMMON SIDE EFFECTS

The most common side effects with TIKOSYN are headache, chest pain, and dizziness (see page 65).

DOSAGE AND ADMINISTRATION

Before TIKOSYN therapy is initiated, the following important guidelines must be followed:

- Therapy with TIKOSYN must be initiated (and, if necessary, re-initiated) in a setting that provides continuous ECG monitoring and in the presence of personnel trained in the management of serious ventricular arrhythmias. Patients should continue to be monitored in this way for a minimum of 3 days or a minimum of 12 hours following electrical or pharmacologic conversion to NSR, whichever period is longer (see page 68).

- The dose must be individualized based on renal function. $\text{CL}_{cr}$ must be calculated based on the Cockcroft-Gault formula for all patients, regardless of serum creatinine value, prior to the first dose of TIKOSYN (see pages 68-71).

- The postdose QTc response to therapy must be measured and the dose adjusted according to the dosing algorithm (see page 71).

- QT interval should be used if heart rate is < 60 beats per minute. There are no data on the use of TIKOSYN when heart rate is < 50 beats per minute (see page 68).
This section reviews information about the epidemiology and consequences of AF. This is provided for background about the disease and is not intended to describe TIKOSYN or its indications.

AF is characterized by rapid, uncoordinated atrial activation that typically occurs in the presence of cardiovascular disease or hypertension. Over time, deteriorating atrial mechanical function places patients at risk for hemodynamic impairment and thromboembolism.

AF may also be seen in association with other arrhythmias such as AFI or atrial tachycardia. AFI is characterized by a sawtooth pattern of regular atrial activation called flutter waves on the ECG. AFI often degenerates into AF and AF may convert to AFI.

AF is a common and persistent dysrhythmia, accounting for about a third of hospitalizations for cardiac arrhythmias. It is estimated that 2.3 million people in the United States are currently diagnosed with AF and this number may rise to 5.6 million by the year 2050. The prevalence of AF in the general population is estimated at 0.4% to 1%. AF prevalence doubles with each decade of life, and by age 80 up to 10% of the population may be diagnosed with AF. AF typically occurs in older patients with a median age for AF patients of 75 years. About one third of AF patients are aged 80 years or older (Fig 1A).

FIGURE 1A. PREVALENCE OF AF IN RELATION TO AGE OF POPULATION

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment initiation education, see DOSAGE AND ADMINISTRATION.

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Long-term data from large epidemiology cohort studies show that the lifetime risk of developing AF is up to 25% for men and women after reaching 40 years of age. The incidence increases over time and reaches 15% for women and 2% for men older than 80 years. Fig 1B illustrates the incidence of AF in 2 US-based epidemiology studies. Most of these data are based on Caucasian populations in North America and Europe. Limited data on the African-American population indicate that AF is less than half of that observed in the Caucasian populations.

AF is associated with significant rates of morbidity and mortality primarily related to the increased risk of stroke as well as heart failure and fatal ventricular arrhythmias. AF is associated with a 2-fold increase in cardiac mortality, which is associated with the severity of underlying heart disease. It is estimated that in patients with AF the risk of stroke is increased 2 to 7 times over the risk of stroke in patients without AF. The risk may be even higher in patients with other cardiovascular (CV) disease, as evidenced by the patients with rheumatic heart disease and AF in the Framingham Heart Study, where stroke risk was observed to be 17-fold greater than age-matched controls.

Important risk factors for AF/AFl include increasing age; male gender; hypertension; diabetes; obesity; hyperthyroidism; and other CV conditions such as valvular heart disease, coronary disease, MI (in men), heart failure, or LV hypertrophy.
TIKOSYN® (dofetilide) is a class III antiarrhythmic agent with a clinical profile studied in more than 5000 patients.

TIKOSYN was shown to be effective in maintaining NSR in 2 large 12-month studies in patients experiencing AF for 1 week to 2 years. In 2 large mortality trials, DIAMOND CHF and DIAMOND MI, TIKOSYN did not adversely affect mortality in patients with significant SHD when initiated in the hospital and administered according to renal function and QTc response to therapy.

TIKOSYN is indicated for the maintenance of NSR (delay in time to recurrence of AF/AFL) in patients with AF/AFL of greater than one week duration who have been converted to NSR. Because TIKOSYN can cause life threatening ventricular arrhythmias, it should be reserved for patients in whom AF/AFL is highly symptomatic. In general, antiarrhythmic therapy for AF/AFL aims to prolong the time in NSR. Recurrence is expected in some patients. TIKOSYN has not been shown to be effective in patients with paroxysmal AF, ventricular tachycardia, or ventricular fibrillation.

TIKOSYN is indicated for the conversion of AF and AFL to NSR. TIKOSYN has not been shown to be effective in patients with paroxysmal AF.

The rest of the monograph discusses key preclinical and clinical characteristics of TIKOSYN as well as information on its appropriate use.

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

Please see full prescribing information and patient information for TIKOSYN® (dofetilide) capsules in back cover pocket.
The chemical name for dofetilide is $N[4-[2-[methyl][2-[4-[(methylsulfonyl)amino]phenoxy]ethyl]amino]ethyl]phenyl]-methanesulfonamide. The empirical formula is $C_{19}H_{27}N_{3}O_{5}S_{2}$, and dofetilide has a molecular weight of 441.6. The structural formula is shown in Figure 2.

Dofetilide is a white to off-white powder. It is very slightly soluble in water and propan-2-ol and is soluble in 0.1M aqueous sodium hydroxide, acetone, and aqueous 0.1M hydrochloric acid.

TIKOSYN capsules contain the following inactive ingredients: microcrystalline cellulose, corn starch, colloidal silicon dioxide, and magnesium stearate. TIKOSYN is supplied for oral administration in 3 dose strengths: 125-mcg (0.125-mg) orange-and-white capsules, 250-mcg (0.25-mg) peach capsules, and 500-mcg (0.5-mg) peach-and-white capsules.

**FIGURE 2. STRUCTURAL FORMULA OF DOFETILIDE**

![Structural formula of dofetilide](data:image/png;base64,iVBORw0KGgoAAAANSUhEUgAAAYAAAAAHCAYAAABhJ4HgAAAgAElEQVR42zHs3QsE...)

**V. PHARMACOLOGY**

**MECHANISM OF ACTION AND ELECTROPHYSIOLOGIC EFFECTS**

**MECHANISM OF ACTION**

TIKOSYN shows Vaughan Williams class III antiarrhythmic activity. The mechanism of action is blockade of the cardiac ion channel carrying the rapid component of the delayed rectifier potassium current, $I_{Kr}$. TIKOSYN is highly potent; the $I_{Kr}$ channel is completely blocked at nanomolar concentrations. TIKOSYN is also very selective. At concentrations covering several orders of magnitude, TIKOSYN blocks only $I_{Kr}$ (associated with class III effect) with no relevant block of the other repolarizing potassium currents (eg, $I_{Ks}$, $I_{K1}$). At clinically relevant concentrations, TIKOSYN has no effect on sodium channels (associated with class I effect), adrenergic alpha-receptors, or adrenergic beta-receptors.
ELECTROPHYSIOLOGY

In a pharmacology study in healthy volunteers, TIKOSYN increased the monophasic action potential duration in a predictable, concentration-dependent manner, primarily due to delayed repolarization. This effect, and the related increase in effective refractory period, is observed in the atria and ventricles in both resting and paced electrophysiologic studies. The increase in QT interval observed on the surface electrocardiogram is a result of prolongation of both effective and functional refractory periods in the His-Purkinje system and the ventricles.

TIKOSYN did not influence cardiac conduction velocity and sinus node function in a variety of studies in patients with or without SHD. This is consistent with a lack of effect of dofetilide on the PR interval and QRS width in patients with preexisting heart block and/or sick sinus syndrome.

In patients, TIKOSYN terminates induced reentrant tachyarrhythmias (eg, AF/AFI and ventricular tachycardia) and prevents their re-induction. TIKOSYN does not increase the electrical energy required to convert electrically induced ventricular fibrillation, and it significantly reduces the defibrillation threshold in patients with ventricular tachycardia and ventricular fibrillation undergoing implantation of a cardioverter-defibrillator device.

HEMODYNAMIC EFFECTS

In hemodynamic studies (Fig 3), TIKOSYN had no effect on cardiac output, cardiac index, stroke volume index, or systemic vascular resistance in patients with ventricular tachycardia, mild-to-moderate CHF or angina, and either normal or low LV ejection fraction (LVEF). There was no evidence of a negative inotropic effect related to TIKOSYN therapy in patients with AF. There was no increase in heart failure in patients with significant LV dysfunction during a median follow-up duration of greater than 1 year. In the overall clinical program, TIKOSYN did not affect blood pressure. Heart rate decreased by 4 to 6 beats per minute.

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

Please see full prescribing information and patient information for TIKOSYN® (dofetilide) capsules in back cover pocket.
In summary, TIKOSYN is a selective blocker of a single potassium channel (I_{Kr}). It has no effect on QRS or blood pressure and has a minimal effect on heart rate (decrease of 4 to 6 beats per minute).

TIKOSYN did not demonstrate negative inotropic effects in hemodynamic and clinical studies.
The pharmacokinetic profile of TIKOSYN in human volunteers and clinical patients is characterized by high (> 90%) bioavailability unaffected by coadministration of food or antacids, linear dose proportionality over the clinical dosing range, low variability both within and between patients, and protein binding of 60% to 70% that is independent of plasma concentration. Because dofetilide is excreted mainly in the urine, primarily as unchanged drug, plasma levels are increased in patients with decreased renal function; accordingly, the dose must be adjusted for renal function. In elderly patients, renal function is often decreased. Because AF affects primarily the elderly, dose adjustment becomes even more important. TIKOSYN undergoes hepatic metabolism, to a small extent, and its pharmacokinetic profile is not affected by mild-to-moderate hepatic dysfunction. However, inhibitors of the CYP3A4 isoenzyme could increase systemic dofetilide exposure. TIKOSYN has a terminal half-life ($t_{1/2}$) of approximately 10 hours, which permits twice daily dosing. The relationship between plasma concentrations of dofetilide and its effect on QTc is linear.

**VI. PHARMACOKINETICS**

**METABOLISM AND EXCRETION**

Approximately 80% of a single dose of TIKOSYN is excreted in urine, of which approximately 80% is excreted as unchanged TIKOSYN; the remaining 20% consists of inactive or minimally active metabolites. Renal elimination involves both glomerular filtration and active tubular secretion (via the cation transport system, a process that can be inhibited by cimetidine, trimethoprim, prochlorperazine, megestrol, and ketoconazole). In vitro studies with human liver microsomes show that dofetilide can be metabolized by CYP3A4 but has a low affinity for this isoenzyme. Moreover, TIKOSYN does not inhibit CYP3A4, CYP2C9, or CYP2D6. However, inhibitors of the CYP3A4 isoenzyme could increase systemic dofetilide exposure.

Metabolites of dofetilide are formed by N-dealkylation and N-oxidation. There are no quantifiable metabolites circulating in plasma, but 5 metabolites have been identified in urine.

**ABSORPTION AND DISTRIBUTION**

The oral bioavailability of dofetilide is > 90%, with maximal plasma concentrations occurring at about 2 to 3 hours in the fasted state. Oral bioavailability is unaffected by food or antacid. The $t_{1/2}$ of TIKOSYN is approximately 10 hours; steady-state plasma concentrations are attained within 2 to 3 days, with an accumulation index of 15 to 20. Plasma concentrations are dose proportional. The plasma protein binding of TIKOSYN is 60% to 70%, is independent of plasma concentration, and is unaffected by renal impairment. The volume of distribution is 3 L/kg.

**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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION. Please see full prescribing information and patient information for TIKOSYN® (dofetilide) capsules in back cover pocket.**
**EFFECT ON QTc**

In a pharmacology study in normal volunteers, increase in QT interval was directly related to dofetilide dose and plasma concentration. Figure 4 shows the relationship between plasma concentrations and increase in QTc. In this study, patients were given dofetilide 1000 mcg BID, and the maximum increase in QTc was observed on day 2. Patients were discontinued from the trial if their QT intervals increased to longer than 600 msec. The increase in QTc attenuated somewhat by day 23 but remained increased compared with baseline. This study is important for 3 reasons. First, looking at the relationship between plasma concentration and increase in QTc on either day 1 or day 23 shows that with an increase in dofetilide plasma concentrations there is a linear increase in mean QTc. Second, the increase in QTc is greater on day 1 than on day 23. Therefore, the maximal QTc prolongation that results from the administration of TIKOSYN occurs during the first few days when the patient is in the hospital being carefully supervised. And third, the shaded area represents the plasma concentrations of dofetilide achieved by the dosing algorithm. This, in turn, gives an estimation of the amount of QTc prolongation one is likely to see when a patient is given dofetilide.

A linear relationship between mean QTc increase and dofetilide dose was also seen in patients with renal impairment, in patients with ischemic heart disease, and in patients with supraventricular and ventricular arrhythmias.

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**FIGURE 4. RELATIONSHIP BETWEEN PLASMA CONCENTRATION OF DOFETILIDE AND CHANGE FROM BASELINE QTc IN YOUNG VOLUNTEERS OVER 23 DAYS**

DATA ON FILE. ³

THE NORMAL RANGE OF DOFETILIDE EXPOSURE ACHIEVED BY THE DOSING ALGORITHM IS INDICATED BY THE SHADOED AREA (1.0–3.5 NG/ML).
The relationship between dose, efficacy, and the increase in QTc from baseline at steady state for the 2 randomized placebo-controlled studies (described further below) is shown in Figure 5. The studies examined the effectiveness of TIKOSYN in conversion to NSR and maintenance of NSR after conversion in patients with AF/AFI of greater than 1 week’s duration. As shown, both the probability of a patient’s remaining in NSR at 6 months and the change in QTc from baseline at steady state of dosing increased in an approximately linear fashion with increasing dose of TIKOSYN. Note that in these studies, doses were modified by results of Clcr measurement and in-hospital QTc prolongation.

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

Please see full prescribing information and patient information for TIKOSYN® (dofetilide) capsules in back cover pocket.
IMPORTANT DRUG-DRUG INTERACTIONS

The concomitant use of verapamil; hydrochlorothiazide (alone or in combinations such as with triamterene); 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 causes 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.

Assessment of a patient’s medication history should include all over-the-counter (OTC), prescription, and herbal or natural preparations, with emphasis on preparations that may affect the pharmacokinetics of TIKOSYN, such as cimetidine, trimethoprim (alone or in combination with sulfamethoxazole) megestrol, ketoconazole, other cardiovascular drugs (especially verapamil), phenothiazines, and tricyclic antidepressants. Hypokalemia or hypomagnesemia may occur with administration of potassium-depleting diuretics, increasing the potential for TdP. A more detailed discussion of drug interactions can be found in the PRECAUTIONS section of the monograph, beginning on page 39.

PHARMACOKINETICS IN SPECIAL POPULATIONS

PATIENTS WITH RENAL IMPAIRMENT

In volunteers with varying degrees of renal impairment and in patients with arrhythmias, the clearance of dofetilide decreases with decreasing CLcr. As a result and as seen in clinical studies, the t1/2 of dofetilide is longer in patients with lower CLcr. Because increases in the QTc interval and the risk of ventricular arrhythmias are directly related to plasma concentrations of dofetilide, dosage adjustment based on calculated CLcr is critically important. Patients with severe renal impairment (CLcr < 20 mL/min) were not included in clinical or pharmacokinetic studies. Studies in which dofetilide 500 mcg was administered orally to normal volunteers and individuals with moderate (CLcr 20-40 mL/min) or severe (CLcr < 20 mL/min) renal dysfunction indicated that maximum concentration (Cmax), area under the curve (AUC), and t1/2 for dofetilide were elevated in patients with renal insufficiency. Thus, dosage adjustment is required based on calculated CLcr.

PATIENTS WITH HEPATIC IMPAIRMENT

There was no clinically significant alteration in the pharmacokinetics of dofetilide in volunteers with mild to moderate hepatic impairment (Child-Pugh class A and B)* compared with age- and weight-matched healthy volunteers. Patients with severe hepatic impairment were not studied.

* Each of 5 variables, encephalopathy grade, ascites, albumin level (in serum), prothrombin time prolongation, and bilirubin level (in serum) is scored from 1 to 3, depending on the degree of abnormality. The 5 scores are summed as follows: Child-Pugh A= 5 or 6, B= 7 to 9, and C= 10 to 15.
PATIENTS WITH HEART DISEASE

Population pharmacokinetic analyses indicate that the plasma concentration of dofetilide in patients with supraventricular and ventricular arrhythmias, ischemic heart disease, or congestive heart failure are similar to those of healthy volunteers, after adjusting for renal function.

THE ELDERLY

After correction for renal function, clearance of dofetilide is not related to age. When single 1000-mcg oral doses of dofetilide were administered to elderly individuals (> 65 years of age), clearance was significantly lower and plasma concentrations were 25% higher than in young healthy male volunteers. This reduced clearance is accounted for by a reduction in renal function in the elderly. Dosage adjustment for older patients, as for younger individuals, should be based on CLcr and QTc response to therapy.

WOMEN

A population pharmacokinetic analysis showed that women have approximately 12% to 18% lower clearance of oral dofetilide than men (14% to 22% greater plasma dofetilide levels) after correction for weight and CLcr. In females, as in males, renal function was the single most important factor influencing dofetilide clearance. In normal female volunteers, hormone replacement therapy (a combination of conjugated estrogens and medroxyprogesterone) did not increase dofetilide exposure.

SUMMARY

Dofetilide is predominantly eliminated by the kidneys. To achieve a therapeutically effective concentration, the dose of dofetilide must be adjusted for renal function. The QTc response to therapy depends on dofetilide plasma concentrations in a predictable fashion. The major factor determining the pharmacokinetics of dofetilide is renal function.

Compared with male patients, female patients have lower clearance of orally administered dofetilide after correction for weight and CLcr.

The concomitant use of verapamil; hydrochlorothiazide (alone or in combinations such as with triamterene); 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 causes 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.

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

Please see full prescribing information and patient information for TIKOSYN® (dofetilide) capsules in back cover pocket.
TIKOSYN IS INDICATED FOR:

MAINTENANCE OF NSR (DELAY IN AF/AFL RECURRENCE)

TIKOSYN is indicated for the maintenance of NSR (delay in time to recurrence of AF/AFl) in patients with AF/AFl of greater than 1 week’s duration who have been converted to NSR. Because TIKOSYN can cause life-threatening ventricular arrhythmias, it should be reserved for patients in whom AF/AFl is highly symptomatic.

In general, antiarrhythmic therapy for AF/AFl aims to prolong the time in NSR. Recurrence is expected in some patients.

CONVERSION OF AF/AFL

TIKOSYN is indicated for the conversion of AF and AFl to NSR.

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

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.

For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION.

TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.
TIKOSYN'S efficacy in the treatment of chronic or persistent AF was evaluated in 2 large multicenter trials. Specifically, the ability to convert patients with AF or AFI of greater than 1 week's duration to NSR and the ability to maintain NSR (delay in time to recurrence of AF/AFI) after drug-induced or electrical cardioversion for up to 12 months was evaluated.

The maintenance of NSR was measured in 3 ways:

1. the probability of remaining in NSR at 6 and 12 months,
2. the percentage of patients who were in NSR and still on treatment at 6 and 12 months, and
3. the time to relapse to AF.

Entry into the trials was limited to those patients who had documented target arrhythmia, no excessive QT prolongation, AV block, or bradycardia. Patients were excluded if there was evidence of acute MI, unstable angina, unstable CHF, reversible causes of the target arrhythmia, or history of polymorphic ventricular tachycardia (PMVT) associated with QT prolonging agents.

EUROPEAN AND AUSTRALIAN MULTICENTER EVALUATIVE RESEARCH ON ATRIAL FIBRILLATION AND DOFETILIDE (EMERALD)

This large-scale, placebo-controlled, randomized, 12-month study, the European and Australian Multicenter Evaluative Research on Atrial Fibrillation and Dofetilide (EMERALD), compared TIKOSYN 500, 250, and 125 mcg administered twice daily with placebo in 534 patients with a primary diagnosis of AF and/or AFI persisting for up to 2 years. Patients' initial doses were adjusted for CLcr and subsequent doses could be adjusted downward according to QTc response to therapy. In all patients, treatment with TIKOSYN was initiated in the hospital.

Patients were hospitalized for the initiation of blinded therapy and had continuous electrocardiographic monitoring during this phase. (Fig 6).

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

Please see full prescribing information and patient information for TIKOSYN (dofetilide) capsules in back cover pocket.
All patients were considered to be at steady state by day 3.

Patients who did not convert to NSR with randomized therapy within 48 to 72 hours had electrical cardioversion. Those patients remaining in NSR after conversion in-hospital were continued on randomized therapy as outpatients (maintenance period) for up to 1 year unless they experienced a recurrence of AF/AFl or withdrew for other reasons.

Patients were randomized to 1 of 4 treatment groups: TIKOSYN 500 mcg BID, 250 mcg BID, or 125 mcg BID, or placebo. Calculated Clcr was used to adjust initial doses downward. The actual numbers of patients who received lower doses are shown in the bottom row of Figure 7. For example, of the 129 patients who were randomized to receive TIKOSYN 500 mcg BID, 96 were administered that dose and 33 were dose adjusted to achieve an equivalent serum exposure (Fig 7).

In all, 22% (88 of 397) had their TIKOSYN dose downtitrated. Increased QT interval or QTc led to discontinuation of therapy in 3% of patients. Please note that all efficacy rates are presented by the dose to which patients were randomized, although some patients may have received a lower dose per the treatment algorithm.
This was a predominantly male population, with an average age of 64. About 50% had SHD and more than 50% were categorized as having NYHA functional class I heart failure. Ninety percent of patients had AF, 10% had AFl. Overall, the mean duration of AF/AFl was 3 months.

There were no clinically meaningful differences in baseline characteristics between the TIKOSYN and placebo groups (Table 1).

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

Please see full prescribing information and patient information for TIKOSYN® (dofetilide) capsules in back cover pocket.
CONVERSION TO NSR IN THE EMERALD TRIAL

TIKOSYN was significantly more effective than placebo in converting patients to NSR (Figs 8 and 9). Conversion was defined as maintenance of NSR for at least 1 hour and still in NSR on day 3. Rates of pharmacologic conversion with TIKOSYN were 29.4% (38/129 patients) randomized to receive 500 mcg BID (P= .001 versus placebo), 10.5% (14/133 patients) receiving 250 mcg BID (P= .001), and 5.9% (8/135 patients) given 125 mcg BID (P= 0.05). Only 1.4% (2/137) of patients assigned to placebo converted to NSR, indicating that these were truly patients with chronic or persistent AF and not paroxysmal AF. The effect of TIKOSYN was rapid: 70% of the patients who converted pharmacologically achieved NSR within 24 to 36 hours of initiation of therapy. Patients not converting pharmacologically were subsequently electronically cardioverted; those not achieving NSR were discontinued from the trial. Ultimately, NSR was achieved in 431 patients (81%).

TABLE 1 EMERALD: BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>TIKOSYN (n=397)</th>
<th>PLACEBO (n=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>266 (67%)</td>
<td>103 (75%)</td>
</tr>
<tr>
<td>Age (mean y)</td>
<td>65</td>
<td>63</td>
</tr>
<tr>
<td>Weight (mean kg)</td>
<td>80</td>
<td>82</td>
</tr>
<tr>
<td>SHD</td>
<td>193 (49%)</td>
<td>71 (52%)</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>208 (52%)</td>
<td>76 (55%)</td>
</tr>
<tr>
<td>II/III</td>
<td>189 (48%)</td>
<td>61 (45%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>185 (47%)</td>
<td>58 (42%)</td>
</tr>
<tr>
<td>Clcr &lt; 60 mL/min</td>
<td>85 (21%)</td>
<td>20 (15%)</td>
</tr>
<tr>
<td>AF</td>
<td>357 (90%)</td>
<td>120 (88%)</td>
</tr>
<tr>
<td>AFI</td>
<td>40 (10%)</td>
<td>17 (12%)</td>
</tr>
<tr>
<td>Median duration of AF/AFI (months)</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

DATA ON FILE.3

Please see full prescribing information and patient information for TIKOSYN® (dofetilide) capsules in back cover pocket.
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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

Please see full prescribing information and patient information for TIKOSYN® (dofetilide) capsules in back cover pocket.
Figure 9 demonstrates the time to pharmacologic conversion for both TIKOSYN 500 mcg BID and placebo. The majority of pharmacologic conversions occurred by 24 to 36 hours.

Efficacy in Preventing Recurrences of AF/AFL (Increased Time to First Recurrence)

TIKOSYN was also significantly more effective than placebo in maintaining patients in NSR. After 6 months of treatment, the probability of remaining in NSR for patients who received TIKOSYN 500 mcg BID and had their dose adjusted, if necessary, was 71%, compared with 26% in patients who received placebo. At the end of 12 months of treatment, the probability of patients on TIKOSYN 500 mcg BID remaining in NSR was 66% versus 21% for placebo (Fig 10). All values for TIKOSYN were significantly higher than for placebo (P<.005). In the patients who converted pharmacologically (30%), the probability of maintaining NSR for 12 months was 76%.
The median time to relapse with TIKOSYN 500 mcg BID was > 365 days compared with 34 days for placebo (P < .001).

The probabilities described above are calculated by Kaplan-Meier analysis, which removes all patients who are discontinued for any reason other than relapse to AF/AFl. Another way to look at the treatment results with TIKOSYN is to look at the number of patients whose therapy was not discontinued for relapse to AF/AFl or other reasons. At 6 months, 57% of patients treated with TIKOSYN 500 mcg BID were still on TIKOSYN and in NSR versus 22% on placebo. At 12 months, 49% of patients receiving 500 mcg BID were still on TIKOSYN and in NSR versus 16% on placebo.

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

Please see full prescribing information and patient information for TIKOSYN® (dofetilide) capsules in back cover pocket.
A second trial supporting the efficacy of TIKOSYN in preventing recurrence of AF/AFl was the Symptomatic Atrial Fibrillation Investigation and Randomized Evaluation of Dofetilide (SAFIRE-D). The primary end point of this trial was the proportion of patients in NSR, as estimated by the Kaplan-Meier method. The design of the double-blind, placebo-controlled trial was similar to that used in EMERALD. The proportion of patients remaining in NSR at 6, 9, and 12 months was evaluated in 325 patients with persistent or chronic AF/AFl of 2 weeks’ to 6 months’ duration.

Baseline demographics for this population were similar to those of EMERALD with the exception of SHD, which was more prevalent in SAFIRE-D. Most patients were categorized as having NYHA functional class II or III (Table 2).

Inclusion and exclusion criteria were similar to those of EMERALD (see page 23).

### TABLE 2. SAFIRE-D: BASELINE CHARACTERISTICS.

<table>
<thead>
<tr>
<th></th>
<th>TIKOSYN (N=241)</th>
<th>PLACEBO (N=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>200 (83%)</td>
<td>73 (87%)</td>
</tr>
<tr>
<td>Age (mean y)</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>Weight (mean kg)</td>
<td>88</td>
<td>89</td>
</tr>
<tr>
<td>SHD</td>
<td>174 (72%)</td>
<td>62 (74%)</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>67 (28%)</td>
<td>22 (26%)</td>
</tr>
<tr>
<td>II/III</td>
<td>172 (72%)</td>
<td>62 (74%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>139 (58%)</td>
<td>47 (56%)</td>
</tr>
<tr>
<td>Clcr &lt; 60 mL/min</td>
<td>81 (34%)</td>
<td>30 (36%)</td>
</tr>
<tr>
<td>AF</td>
<td>210 (87%)</td>
<td>67 (80%)</td>
</tr>
<tr>
<td>AFl</td>
<td>31 (13%)</td>
<td>17 (20%)</td>
</tr>
<tr>
<td>Median duration of AF/AFl (months)</td>
<td>148</td>
<td>141</td>
</tr>
</tbody>
</table>

DATA ON FILE.³
In contrast to EMERALD, more patients in this study were treated with digoxin, diuretics, beta blockers, and ACE inhibitors. These findings reflect a population with more advanced CV disease relative to EMERALD; 72% of patients were in NYHA classes II and III (Tables 2 and 3).

Patients were randomized to 1 of 4 treatment groups, TIKOSYN 500 mcg BID, 250 mcg BID, or 125 mcg BID, or placebo, and the dose could be adjusted for both baseline CLcr and QTc prolongation. The initial dose of TIKOSYN was based on the calculated CLcr using the Cockcroft-Gault formula. Increased QT interval or QTc led to discontinuation of therapy in 3% of patients.

**TABLE 3. SAFIRE-D: CONCOMITANT MEDICATIONS AT ENTRY**

<table>
<thead>
<tr>
<th></th>
<th>TIKOSYN (N=241)</th>
<th>PLACEBO (N=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>197 (82%)</td>
<td>67 (80%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>116 (48%)</td>
<td>45 (54%)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>101 (42%)</td>
<td>43 (51%)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>53 (22%)</td>
<td>21 (25%)</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>71 (29%)</td>
<td>20 (24%)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>225 (93%)</td>
<td>77 (92%)</td>
</tr>
</tbody>
</table>

ACE=ANGIOTENSIN-CONVERTING ENZYME,
DATA ON FILE.3

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

Please see full prescribing information and patient information for TIKOSYN® (dofetilide) capsules in back cover pocket.
Actual doses received and patient numbers are shown in the lower portion of Figure 11.

In this trial, treatment was initiated in-hospital, and patients remained hospitalized for 3 days.

To qualify as a successful conversion, patients had to achieve and maintain NSR for at least 24 hours.
CONVERSION TO NSR IN SAFIRE-D

TIKOSYN 500 mcg BID was significantly more effective than placebo in converting patients to NSR (Figs 12 and 13). Successful conversion occurred in 29.9% (23/77) of those randomized to receive 500 mcg BID (P<.001), 9.8% (8/82) of patients who received 250 mcg BID (P=.015), and 6.1% (5/82) of those who received 125 mcg BID (P=.098). Only 1.2% (1/84) of patients given placebo converted to NSR, again indicating that this was a population with chronic or persistent AF.

In those patients with AF/AFL who successfully converted to NSR with TIKOSYN 500 mcg BID (29.9%), most converted within 24 to 36 hours of start of therapy.

Conversion to NSR with TIKOSYN was rapid. Among those patients achieving cardioversion with TIKOSYN, 70% of the patients achieved NSR within 24 hours and 93% within the initial 36 hours of initiation of therapy. Patients not converting pharmacologically were electrically cardioverted. Patients who maintained NSR for more than 24 hours were entered into the maintenance phase of the study and patients not achieving NSR were discontinued from the trial. Combined conversion to NSR for TIKOSYN and placebo groups was achieved in 251 patients (77%).

Although fewer TIKOSYN patients required electrical cardioversion, the total number of patients achieving NSR with the combination of pharmacologic and electrical cardioversion was similar in the TIKOSYN and placebo treatment groups. Relapse, an end point event, was defined as recurrence of AF/AFL lasting longer than 24 hours.

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

Please see full prescribing information and patient information for TIKOSYN® (dofetilide) capsules in back cover pocket.
SAFIRE-D was a multicenter trial of 325 patients with primary diagnoses of AF and/or AFl persisting for up to 6 months. The chart represents conversion to NSR in patients randomized to receive TIKOSYN 500 mcg BID (n=77) or placebo (n=84). Conversion was defined as maintenance of NSR for at least 24 hours.

Please see full prescribing information and patient information for Tikosyn® (dofetilide) capsules in back cover pocket.
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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

Please see full prescribing information and patient information for TIKOSYN® (dofetilide) capsules in back cover pocket.
EFFICACY IN PREVENTING RECURRENCE OF AF/AFL (INCREASED TIME TO RECURRENCE)

TIKOSYN was significantly more effective than placebo at maintaining this type of patient population in NSR during the 1-year SAFIRE-D trial. After 6 months of treatment, the probability of remaining in NSR was 62% for patients who received TIKOSYN 500 mcg BID and 37% for those who received placebo. At the end of 12 months of treatment, the respective probabilities of remaining in NSR were 58% and 25% for patients assigned to TIKOSYN 500 mcg BID or placebo (Fig 14). These results were significantly different from placebo ($P = .001$). The probability of maintaining NSR for 12 months was 80% in those patients converting pharmacologically with TIKOSYN 500 mcg BID.

The figure shows maintenance rates up to 12 months for those achieving NSR. Rhythm status was determined by ECG.

<table>
<thead>
<tr>
<th></th>
<th>NSR AT 12 MONTHS (%)</th>
<th>NOMINAL P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIKOSYN 500 MCG BID</td>
<td>58</td>
<td>.001</td>
</tr>
<tr>
<td>TIKOSYN 250 MCG BID</td>
<td>37</td>
<td>.104</td>
</tr>
<tr>
<td>TIKOSYN 125 MCG BID</td>
<td>40</td>
<td>.208</td>
</tr>
<tr>
<td>PLACEBO</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

Please see full prescribing information and patient information for TIKOSYN® (dofetilide) capsules in back cover pocket.
SUMMARY

The results of 2 large-scale well-controlled clinical trials involving patients treated with TIKOSYN showed that TIKOSYN effectively and rapidly converted approximately 30% of patients with AF or AFl to NSR during the initiation phase of therapy, thus reducing their need for electrical cardioversion. The recommended dosage of TIKOSYN, 500 mcg BID, adjusted for Clcr and QTc response to therapy, was significantly (P<.001) superior to placebo at maintaining patients with AF or AFl in NSR after 12 months of treatment. At 12 months, the probabilities of remaining in NSR were 58% and 66% for patients given TIKOSYN compared with 25% and 21% of those given placebo (P<.001).

At 12 months, 46% and 49% of patients were still in NSR and still on TIKOSYN compared with 22% and 16% on placebo.

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

Please see full prescribing information and patient information for TIKOSYN® (dofetilide) capsules in back cover pocket.
**BOXED WARNING**

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.

For detailed instructions regarding dose selection, see DOSE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSE AND ADMINISTRATION.

**CONTRAINDICATIONS**

TIKOSYN is contraindicated in the following clinical conditions:

- Patients with congenital or acquired long QT syndromes
- Patients with a baseline QT interval or QTc > 440 msec (500 msec in patients with ventricular conduction abnormalities)
- Patients with severe renal impairment (Clcr < 20 mL/min).

The concomitant use of TIKOSYN and the following drugs is contraindicated:

- Verapamil
- The cation transport system inhibitors cimetidine, trimethoprim (alone or in combination with sulfamethoxazole), or ketoconazole, as each of these drugs causes a substantial increase in dofetilide plasma concentrations.
- Hydrochlorothiazide (alone or in combinations such as with triamterene) with TIKOSYN is contraindicated (see PRECAUTIONS, Drug-Drug Interactions) because this has been shown to significantly increase dofetilide plasma concentrations and QT interval prolongation.

In addition, other known inhibitors of the renal cation transport system such as prochlorperazine and megestrol should not be used in patients on TIKOSYN.

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

**WARNINGS**

**VENTRICULAR ARRHYTHMIA**

TIKOSYN can cause serious ventricular arrhythmias, primarily 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 Clcr or certain TIKOSYN drug interactions will increase dofetilide plasma concentration. The risk of TdP can be reduced by controlling the plasma concentration through adjustment of the initial TIKOSYN dose according to Clcr and by monitoring the ECG for excessive increases in the QT interval.

Treatment with TIKOSYN must, therefore, be started only in patients placed for a minimum of 3 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 CLcr for all patients must precede administration of the first dose of TIKOSYN. In clinical studies, the risk of dofetilide-induced ventricular arrhythmia was assessed in 3 ways:

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, and
3) by observing the overall mortality rate in patients with AF and in patients with SHD.

1. RELATION OF QT INTERVAL TO DOSE

The QT interval increases linearly with increasing TIKOSYN dose (as can be seen in Fig 5, page 17).

2. FREQUENCY OF TdP

In the SVA population (patients with AF and other SVAs evaluated in 10 double-blind placebo-controlled clinical trials), the overall incidence of TdP for all doses was 0.8%. At the recommended TIKOSYN dosage of 500 mcg BID, the frequency of TdP was 0.9% (6/703 patients). The rate of TdP was reduced when patients were dosed according to their renal function. A similar percent reduction, following the introduction of dosing according to renal function, was seen in the DIAMOND trials (see page 60).

In clinical trials, the majority of the episodes of TdP occurred within the first 3 days of TIKOSYN therapy. Although the majority of these events occurred while patients were hospitalized and promptly treated, a small number occurred following the hospitalization phase.

3. MORTALITY

In a pooled survey analysis of patients in the SVA population (low prevalence of SHD), 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 SHD, 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 significant SHD (LVEF≤35%). In these large-scale, double-blind studies, the 1-year mortality rates were 36% (541/1511 patients) with TIKOSYN and 37% (560/1517 patients) with placebo. In an analysis of 506 very-high-risk DIAMOND patients with both significant SHD and AF/AFl at baseline, 1-year mortality on TIKOSYN was 31% versus 32% on placebo. Survival results from all these studies follow.

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

Please see full prescribing information and patient information for TIKOSYN® (dofetilide) capsules in back cover pocket.
Because of the small number of events in the pooled survival analysis of placebo-controlled trials in patients with SVAs, an excessively high rate of mortality due to TIKOSYN cannot be ruled out with confidence. However, it is reassuring that in 2 large-scale placebo-controlled mortality studies of patients with significant SHD (DIAMOND CHF and DIAMOND MI) there were no more deaths among TIKOSYN-treated patients than among patients given placebo.

Although TIKOSYN produced a dose-dependent increase in both QTc and TdP, when it was initiated according to the recommended dosing algorithm, the incidence of TdP was reduced, and no excess mortality was observed.

DRUG-DRUG INTERACTIONS

TIKOSYN is eliminated both by hepatic metabolism (20\%) and renal excretion as unchanged drug (80\%). 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 (TdP). 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 3 inhibitors of this process have been shown to increase systemic dofetilide exposure. The magnitude of the effect on renal elimination by cimetidine, trimethoprim (alone or in combination with sulfamethoxazole), and ketoconazole (all contraindicated concomitant uses with dofetilide) suggest 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 TdP. Potassium levels should be within the normal range prior to administration of TIKOSYN and maintained in the normal range during administration of TIKOSYN (see DOSAGE AND ADMINISTRATION).

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 3 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 3 months.
PRECAUTIONS

RENAL IMPAIRMENT

The overall systemic clearance of TIKOSYN is decreased and plasma concentration increased with reduction of CL\textsubscript{cr}. The dose of TIKOSYN must be adjusted based on CL\textsubscript{cr} and not serum creatinine. Adjustment of dosing based on CL\textsubscript{cr} rather than serum creatinine levels is particularly important in elderly patients with AF. AF is primarily a disease of the elderly, and older patients may have apparently normal levels of serum creatinine but reduced CL\textsubscript{cr}. 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 CL\textsubscript{cr}, 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 TIKOSYN on conduction velocity. No effect on AV nodal conduction following TIKOSYN treatment was noted in normal volunteers or 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). The incidence of conduction disturbance occurred at a rate no different from placebo.

INFORMATION FOR PATIENTS

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.

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

Please see full prescribing information and patient information for TIKOSYN® (dofetilide) capsules in back cover pocket.
MEDICATIONS AND SUPPLEMENTS
Assessment of patients’ medication history should include all OTC, 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 (especially verapamil), phenothiazines, and tricyclic antidepressants. If a patient is taking TIKOSYN and requires antiulcer 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 OTC, 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 OTC preparation (Table 4).

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 INTERACTION
There are no known drug/laboratory test interactions for TIKOSYN.

### TABLE 4. IMPORTANT INFORMATION FOR PATIENTS

<table>
<thead>
<tr>
<th>PATIENTS SHOULD:</th>
<th>PATIENTS SHOULD NOT:</th>
</tr>
</thead>
<tbody>
<tr>
<td>■ Read patient package insert (prior to TIKOSYN initiation and at renewals)</td>
<td>■ Take cimetidine, ketoconazole, verapamil, trimethoprim (alone or in combination with sulfamethoxazole), prochlorperazine, or megestrol during TIKOSYN therapy or hydrochlorothiazide (alone or in combinations such as with triamterene)</td>
</tr>
<tr>
<td>■ Be fully instructed on compliance, drug interactions, and monitoring requirements</td>
<td>■ Double the next dose if a dose is missed</td>
</tr>
<tr>
<td>■ Report use of all OTC and prescription (Rx) medications, indicating any changes in use</td>
<td></td>
</tr>
<tr>
<td>■ Inform prescribers of ongoing TIKOSYN therapy</td>
<td></td>
</tr>
<tr>
<td>■ Immediately report symptoms of electrolyte imbalance</td>
<td></td>
</tr>
</tbody>
</table>

DATA ON FILE.³
DRUG-DRUG INTERACTIONS

TIKOSYN has significant interactions with certain drugs that interfere with either its hepatic metabolism or renal excretion. Accordingly, it should be emphasized that because coadministration of verapamil or the cation transport system inhibitors, such as cimetidine, hydrochlorothiazide, trimethoprim (alone or in combination with sulfamethoxazole), or ketoconazole, along with TIKOSYN raises peak or total plasma dofetilide concentrations to levels that place the patient at an unacceptably high risk for the development of TdP, concomitant use of these agents is contraindicated.

CIMETIDINE

Concomitant use of TIKOSYN and cimetidine is contraindicated. In addition to its effect on hepatic metabolism, cimetidine is a potent inhibitor of renal tubular secretion (the primary method of dofetilide elimination). Coadministration of cimetidine reduces renal tubular secretion of dofetilide.

Cimetidine at 400 mg BID (the usual prescription dosage) coadministered with TIKOSYN (500 mcg BID) for 7 days has been shown to increase dofetilide plasma levels by 58%. Cimetidine at dosages of 100 mg BID (OTC) 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 antiulcer therapy, it is suggested that omeprazole, ranitidine, or antacids (aluminum and magnesium hydroxides) be used as alternatives to cimetidine.

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION. Please see full prescribing information and patient information for TIKOSYN° (dofetilide) capsules in back cover pocket.

VERAPAMIL

Concomitant use of TIKOSYN and verapamil is contraindicated. Coadministration 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 SVA and DIAMOND patient populations, the concomitant administration of verapamil with dofetilide was associated with a higher occurrence of TdP.
KETOCONAZOLE

Concomitant use of TIKOSYN and ketoconazole is contraindicated. Ketoconazole at 400 mg QD (the maximum approved prescription dose) coadministered 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 43% in males and 69% in females.

Coadministration of ketoconazole affects both the renal and nonrenal clearance of dofetilide (Fig. 15). It reduces total clearance of dofetilide by 34.7%, renal clearance by 31.3%, and nonrenal clearance by 40.3%. Ketoconazole is a potent inhibitor of CYP3A4, and the magnitude of its effect on the pharmacokinetics of TIKOSYN most probably represents the maximum effect likely to be observed with a drug that inhibits this isoenzyme. Since ketoconazole reduces the nonrenal clearance of dofetilide by slightly less than 50% and nonrenal clearance constitutes about 38% of the total dofetilide clearance, this amounts to an approximate 15% reduction in total clearance attributed to the metabolic effect of ketoconazole.

These results provide a frame of reference when considering the potential impact of other inhibitors of CYP3A4 on TIKOSYN pharmacokinetics. It is important to note that ketoconazole also has a substantial effect on the renal clearance of dofetilide, and that this may be due to effects on renal cationic secretion.
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 coadministered BID with TIKOSYN (500 mcg BID) for 4 days has been shown to increase dofetilide AUC by 103% and $C_{\text{max}}$ 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 coadministered 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 $C_{\text{max}}$ by 21%. However, the pharmacodynamic effect increased by 19% (QTc increase over time) and by 95% (maximum QTc increase). In patients receiving HCTZ in combination with triamterene, dofetilide AUC increased by 30% and $C_{\text{max}}$ by 15%. However, the pharmacodynamic effect increased by 39% (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 with 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 nonsignificantly reduced relative risk of 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 (eg, triamterene, metformin, and amiloride) should be coadministered 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 (eg, macrolide antibiotics, azole antifungal agents, protease inhibitors, serotonin reuptake inhibitors, amiodarone, cannabinoids, diltiazem, grapefruit juice, nefazodone, norfloxacin, quinine, and zafirlukast) should be cautiously coadministered with TIKOSYN as they can potentially increase dofetilide levels. Dofetilide is not an inhibitor of CYP3A4 or of other cytochrome P450 isoenzymes (eg, CYP2C9, CYP2D6) and is not expected to increase levels of drugs metabolized by CYP3A4.

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

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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 TIKOSYN was associated with a higher occurrence of TdP. It is unclear whether this represents an interaction with TIKOSYN or the presence of more severe SHD in patients on digoxin; SHD 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, amlopidine, phenytoin, glyburide, ranitidine, omeprazole, hormone replacement therapy (a combination of conjugated estrogens and medroxyprogesterone), antacids (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 BID), phenytoin, theophylline, or oral contraceptives (Table 5).

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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 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 test of cytogenetic aberrations in vivo in mouse bone marrow and in vitro in human lymphocytes. Rats and mice treated with dofetilide in their diet for 2 years showed no evidence of an increased incidence of tumors compared with controls. The highest dofetilide dosage administered for 24 months was 10 mg/kg/day to rats and 20 mg/kg/day to mice. Mean dofetilide AUCs (0-24 hours) 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 10 mg/kg/day, a dose that would be expected to provide a mean dofetilide AUC(redacted) 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, respectively) were associated with mean dofetilide AUCs that were about 4, 13, and 3 times the maximum likely human AUC, respectively.

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

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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 dosages of ≥2 mg/kg/day. Other than an increased incidence of nonossified 5th metacarpal, and the occurrence of hydroureter and hydronephroses at dosages as low as 1 mg/kg/day in the rat, structural anomalies associated with drug treatment were not observed in either species at dosages below 2 mg/kg/day. The clearest drug-effect associations were for sternebral 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 (0-24 hours) 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 for whom 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 CLcr, 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 TdP, TIKOSYN was associated with a greater risk of TdP in female patients than in male patients. During the TIKOSYN clinical development program, the risk of TdP in women was approximately 3 times the risk in males. Unlike TdP, 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 women on TIKOSYN compared with women on placebo.

PEDIATRIC USE

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

ANALYSIS OF SURVIVAL AND PROARRHYTHMIC AND OTHER CLINICAL ADVERSE EVENTS

The clinical program for the oral formulation of TIKOSYN involved 5557 patients who varied substantially in their degree of SHD, and thereby in their potential for experiencing serious CV adverse events.
Analysis of survival and proarrhythmic events, particularly TdP, was carried out in 3 distinct populations (Fig 16).

**FIGURE 16. SUMMARY OF PATIENT POPULATIONS EVALUATED FOR SAFETY IN THE TIKOSYN CLINICAL PROGRAM**

- **ORAL PROGRAM**
  - **SVA TRIALS**
    - \( n=2023 \)
    - (LOW-TO - MODERATE SHD)
  - **DIAMOND MORTALITY TRIALS (CHF & MI)**
    - \( n=3028 \)
    - (SIGNIFICANT SHD)
  - **DIAMOND AF**
    - \( n=506 \)
    - (SIGNIFICANT SHD)

CHF=CONGESTIVE HEART FAILURE.
DATA ON FILE.³

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

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The SVA population comprised 2023 patients who had low- to- moderate risk for SHD and were treated in 10 double-blind, placebo-controlled trials of TIKOSYN (Table 6).

**TABLE 6. SUMMARY OF BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS TREATED IN POOLED SVA TRIALS OF TIKOSYN**

<table>
<thead>
<tr>
<th></th>
<th>TIKOSYN (n=1346)</th>
<th>PLACEBO (n=677)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>889 (66%)</td>
<td>438 (65%)</td>
</tr>
<tr>
<td>Age (mean y)</td>
<td>64</td>
<td>62</td>
</tr>
<tr>
<td>SHD</td>
<td>731 (54%)</td>
<td>397 (59%)</td>
</tr>
<tr>
<td>CHF</td>
<td>147 (11%)</td>
<td>81 (12%)</td>
</tr>
<tr>
<td>NYHA class II/III/IV</td>
<td>479 (39%)*</td>
<td>234 (39%)*</td>
</tr>
<tr>
<td>MI</td>
<td>130 (10%)</td>
<td>87 (13%)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>692 (51%)</td>
<td>319 (47%)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>285 (21%)</td>
<td>149 (22%)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>395 (29%)</td>
<td>206 (30%)</td>
</tr>
</tbody>
</table>

*For NYHA class: TIKOSYN 1229, PLACEBO 602. Data on file. 3*

It is important to note that, even in the SVA population, 54% (n=731) had SHD, 11% (n=147) had CHF, 39% (n=479)* demonstrated NYHA class II or III heart failure, and 10% (n=30) had a previous MI.

A second group consisted of 3028 higher-risk patients with significant SHD treated in the DIAMOND CHF and MI trials. The 2 DIAMOND studies were large-scale mortality studies conducted in Denmark that included populations with impaired LV function (equivalent to an LVEF ≤35%) and either an acute episode of CHF (DIAMOND CHF) or a recent MI (DIAMOND MI). These 3-year trials were designed primarily to determine whether treatment with TIKOSYN decreased mortality in these patient populations with significant cardiac disease that were at risk for unexpected cardiac death.
The clinical and demographic characteristics of the patients in the DIAMOND trials are summarized in Table 7.

**TABLE 7. BASELINE CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF PATIENTS IN THE DIAMOND CHF AND MI TRIALS**

<table>
<thead>
<tr>
<th></th>
<th>DIAMOND CHF (N=762)</th>
<th></th>
<th>DIAMOND MI (N=749)</th>
<th></th>
<th>PLACEBO (N=761)</th>
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<tbody>
<tr>
<td>Male</td>
<td>72 %</td>
<td></td>
<td>72 %</td>
<td></td>
<td>76 %</td>
<td></td>
</tr>
<tr>
<td>Age (mean y)</td>
<td>70</td>
<td></td>
<td>68</td>
<td></td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>NYHA class III</td>
<td>56 %</td>
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<td>30 %</td>
<td></td>
<td>32</td>
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</tr>
<tr>
<td>NYHA class IV</td>
<td>7 %</td>
<td></td>
<td>5 %</td>
<td></td>
<td>4</td>
<td></td>
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<tr>
<td>LVEF (median)</td>
<td>27</td>
<td></td>
<td>33</td>
<td></td>
<td>33</td>
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<tr>
<td>Previous MI</td>
<td>51 %</td>
<td></td>
<td>36 %</td>
<td></td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>63 %</td>
<td></td>
<td>28 %</td>
<td></td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Beta blockers</td>
<td>9 %</td>
<td></td>
<td>36 %</td>
<td></td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>72 %</td>
<td></td>
<td>59 %</td>
<td></td>
<td>57</td>
<td></td>
</tr>
</tbody>
</table>

DATA ON FILE.3

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

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The third study population (DIAMOND AF) consisted of 506 patients enrolled in the DIAMOND trials (391 patients from the DIAMOND CHF study and 115 patients from DIAMOND MI) who had coexistent AF/AFl at study entry and significant levels of SHD (Table 8).

### TABLE 8. BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE DIAMOND AF POPULATION

<table>
<thead>
<tr>
<th></th>
<th>TIKOSYN (N=249)</th>
<th>PLACEBO (N=257)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>188 (76%)</td>
<td>201 (78%)</td>
</tr>
<tr>
<td>Age (mean y)</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>122 (52%)*</td>
<td>126 (49%)*</td>
</tr>
<tr>
<td>NYHA class IV</td>
<td>16 (6%)*</td>
<td>19 (7%)*</td>
</tr>
<tr>
<td>LVEF&lt; 25%</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>MI</td>
<td>93 (37%)</td>
<td>104 (40%)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>229 (92%)</td>
<td>228 (89%)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>29 (12%)</td>
<td>32 (13%)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>166 (67%)</td>
<td>163 (63%)</td>
</tr>
</tbody>
</table>

*N FOR NYHA CLASS: TIKOSYN 233, PLACEBO 255.
DATA ON FILE.3

The following section examines in depth the 3 primary safety measures – survival, proarrhythmic events (TdP), and other clinical adverse events – evaluated in these study populations (Table 9).

### TABLE 9. PATIENT POPULATIONS EVALUATED FOR SURVIVAL, PROARRHYTHMIC EVENTS, AND/OR OTHER CLINICAL ADVERSE EVENTS IN THE TIKOSYN CLINICAL PROGRAM

<table>
<thead>
<tr>
<th>STUDY</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled SVA (moderate SHD)</td>
<td>2023</td>
</tr>
<tr>
<td>DIAMOND CHF and MI (significant SHD)</td>
<td>3028</td>
</tr>
<tr>
<td>DIAMOND AF (significant SHD)</td>
<td>506</td>
</tr>
</tbody>
</table>

DATA ON FILE.3
SURVIVAL

TIKOSYN therapy had no deleterious effects on survival in any of the populations evaluated. The safety of TIKOSYN in these patients was due, at least in part, to adherence to the dosing algorithm. First, all therapy was initiated in a hospital; second, the dosing regimen achieved equivalent plasma drug concentrations for patients with differing renal function; and third, patients with particular sensitivity to QTc-prolonging agents were identified and their TIKOSYN dose was reduced or discontinued. Treatment was carefully initiated in a hospital setting, where adverse events such as TdP could be readily managed. Identification of, and discontinuation of treatment for, patients at potentially increased risk for adverse events associated with QTc prolongation contributed significantly to the reduction of TdP incidences. A small incidence of TdP remained, and, although the majority of these events occurred while patients were hospitalized and promptly treated, a small number occurred following hospitalization phase.

POOLED SVA POPULATION

Treatment with TIKOSYN had no significant effect on survival among the patients treated in the SVA trials. The overall survival rate for the patients treated with TIKOSYN was 99.1% (1334/1346 patients) and that for the patients who received placebo was 99.6% (674/677 patients). Kaplan-Meier analysis revealed no significant survival difference between groups. However, given the small number of events, there were wide confidence intervals around the point estimate of survival (Fig 17).

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

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A survival analysis based on data pooled from 10 randomized placebo-controlled trials in SVA patients. Percent of patients surviving longer than 540 days is displayed for patients receiving placebo or TIKOSYN. Hazard ratio (TIKOSYN:placebo) was 1.1 adjusted for duration of therapy, primary diagnosis, age, gender, and prevalence of SHD.
DIAMOND POPULATIONS

DIAMOND CHF studied 1538 patients hospitalized with moderate to severe (60% NYHA class III or IV) CHF who had confirmed impaired LV function (ejection fraction ≤35%). DIAMOND MI studied 1510 patients hospitalized with recent (2-7 days) MI and heart failure (40% NYHA class III or IV) who had confirmed impaired LV function (ejection fraction ≤35%). The clinical and demographic characteristics of the patients in the DIAMOND trials are summarized in Table 7 (see page 49).

Treatment of patients in the DIAMOND studies was initiated in the hospital under monitored conditions and patients remained under telemetric observation of rhythm and heart rate for at least the first 3 consecutive days of interrupted medication. Patients were randomized to either TIKOSYN 500 mcg BID or placebo. However, the dose actually delivered to a given patient was determined by the individual’s renal function. Patients with a calculated CLcr of 40 to 60 mL/min, with AF/AFl at baseline, or if QT-interval prolongation occurred after dosing (> 550 msec or > 20% increase from baseline) were given 250 mcg BID or matched placebo, and those with CLcr < 40 mL/min were given 250 mcg QD. Further dosage adjustments to the minimum of 250 mcg QD were made as necessary for excessive QTc prolongation or adverse events. Patients could be discharged after 3 days of study medication in the hospital, but for many, their underlying condition required a more prolonged stay. After discharge, patients were seen again at month 1 month 3, and at 3-month intervals after randomization of the final recruit. The observation period was approximately 3 years.

In addition, results in the subset of patients with AF in the DIAMOND trials provide further evidence of safety in a very-high-risk population of patients with SHD accompanying AF. Note, however, that this AF population was given a lower (250 mcg BID) dosage (see DIAMOND patients with AF).

DIAMOND CHF POPULATION

ALL-CAUSE MORTALITY

In DIAMOND CHF (see above), patients received a median duration of therapy of greater than 1 year. The probability of survival at 1 year was 73% (95% CI: 0.70-0.77) in the TIKOSYN group and 72% (95% CI: 0.69-0.75) in the placebo group (hazard ratio 0.94, 95% CI: 0.81-1.11, P= .56) (Fig 18). At the end of this 3-year study, there were 311 deaths among patients randomized to TIKOSYN (n= 762) and 317 among those randomized to placebo (n= 756).

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

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CAUSE-SPECIFIC MORTALITY

No statistically significant differences between TIKOSYN and placebo were detected for most secondary end points, including cardiac mortality and incidence of total arrhythmic mortality. The confirmation of death due to cardiac causes was based on the Events Committee assessment. The Events Committee provided an assessment for each death as either cardiac or noncardiac, and in cases where the cause of death could not be classified, the death was defined as cardiac. At 1 year, the probability of survival was 71.5% in the TIKOSYN group and 76.6% in the placebo group (log rank $P = .89$).

The confirmation of death due to arrhythmia (presumed or documented) was also based on the Events Committee assessment. The Events Committee provided an assessment for each cardiac death as either arrhythmic or nonarrhythmic. In cases where death could not be classified as either cardiac/noncardiac or as arrhythmic/nonarrhythmic, the death was defined as arrhythmic. At 1 year, the probability of survival was 85.5% in the TIKOSYN group and 86.0% in the placebo group (log rank $P = .97$).
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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

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DIAMOND MI POPULATION

ALL-CAUSE MORTALITY
In DIAMOND MI (see page 53), patients received a median duration of therapy of greater than 1 year. The probability of survival at 1 year was 79% (95% CI: 0.76-0.82) in the TIKOSYN group and 77% (95% CI: 0.74-0.80) in the placebo group (hazard ratio = 0.97, 95% CI: 0.80-1.17, \( P = .23 \)) (Fig 20). At the end of 3 years, there were 230 deaths among patients randomized to TIKOSYN (n= 749) and 243 among patients randomized to placebo (n= 761).

CAUSE-SPECIFIC MORTALITY
No statistically significant differences between TIKOSYN and placebo were detected for most secondary end points, including cardiac mortality and incidence of total arrhythmic mortality. The definition of cardiac mortality was also the same as that used in DIAMOND CHF. At 1 year, the probability of survival was 81% in the TIKOSYN group and 79% in the placebo group (log rank \( P = .101 \)).

The definition of arrhythmic mortality was also the same as that used in DIAMOND CHF. At 1 year, the probability of survival was 87% in the TIKOSYN group and 86% in the placebo group (log rank \( P = .139 \)).
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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

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**ALL-CAUSE HOSPITALIZATION**

In all, 371/749 (50%) patients on TIKOSYN and 439/761 (55%) on placebo required hospitalization. Of these, 200/749 (27%) patients on TIKOSYN and 201/761 (26%) on placebo required hospitalization because of worsening heart failure.

As noted above, the DIAMOND trials were intended to determine whether TIKOSYN could reduce the risk of unexpected death in patients (with significant SHD) at high risk for this event. The trials did not demonstrate a reduction in mortality; however, they provide reassurance that, when initiated carefully in a hospital or equivalent setting, TIKOSYN did not increase mortality rates in patients with significant SHD. This is an important finding because other antiarrhythmics (notably the class IC antiarrhythmics studied in the Cardiac Arrhythmia Suppression Trial [CAST] and a pure class III antiarrhythmic, d-sotalol [SWORD]) have increased mortality rates in post-MI populations. The DIAMOND trials, therefore, provide evidence of a method of reducing the TIKOSYN-related adverse events in a population susceptible to ventricular arrhythmias.

**DIAMOND AF POPULATION**

There were 506 patients in the 2 DIAMOND studies who had AF at entry (249 randomized to TIKOSYN and 257 randomized to placebo). DIAMOND AF patients randomized to TIKOSYN received 250 mcg BID. The dose for these patients was adjusted for renal function using the algorithm displayed in Table 10.

Sixty-five percent of these AF patients had impaired renal function ($\text{Cl}_{\text{Cr}} < 60 \text{ mL/min}$), so that TIKOSYN 250 mcg BID represents the dosage they would have received in the AF trials, which would give drug exposure similar to a person with normal renal function given 500 mcg BID. In the DIAMOND AF–subpopulation there were 111 deaths (45%) in the 249 patients in the TIKOSYN group and 116 deaths (45%) in the 257 patients in the placebo group (hazard ratio = 1.01, 95% CI: 0.78-1.32, $P = .94$; Fig 21).

<table>
<thead>
<tr>
<th>$\text{Cl}_{\text{Cr}}$ (mL/min)</th>
<th>$\geq 60$</th>
<th>40-60</th>
<th>20-&lt; 40</th>
<th>&lt; 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>In AF/AFL</td>
<td>250 mcg</td>
<td>250 mcg</td>
<td>250 mcg</td>
<td>excluded</td>
</tr>
<tr>
<td>BID</td>
<td>BID</td>
<td>QD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In DIAMOND AF patients with impaired renal function, there was no difference in mortality in those receiving TIKOSYN compared with those receiving placebo.

HOSPITALIZATION

Hospital readmission rates for any reason were 125/249 patients, or 50%, on TIKOSYN and 156/257 patients, or 61%, for placebo. Of these, readmission rates for worsening heart failure were 73/249 patients, or 29%, on TIKOSYN and 102/257 patients, or 40%, for placebo (Fig 22).

SUMMARY

The results of the survival analyses for the SVA, DIAMOND CHF, DIAMOND MI, and DIAMOND AF populations indicate that TIKOSYN therapy did not adversely affect survival in a wide range of patients, many of whom had significant SHD. 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 SVA. However, it is reassuring that in 2 large-scale placebo-controlled mortality studies in patients with significant heart disease (DIAMOND-CHF/MI) there was no excess mortality in TIKOSYN-treated patients compared with patients given placebo.

These findings are important because other antiarrhythmics (notably the class IC antiarrhythmics studied in the CAST and a pure class III antiarrhythmic, d-sotalol [SWORD]), have increased mortality in postinfarction populations. The DIAMOND trials, therefore, provide evidence of the importance of adhering to the dosing and initiation principles.
TIKOSYN therapy did not adversely affect survival in a wide range of patients, many of whom had significant SHD.

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

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**FIGURE 22. DIAMOND AF: HOSPITALIZATION FOR WORSENING CHF**

Probabilities of patients not requiring hospitalization over 3 years are displayed for both treatment groups in DIAMOND AF. “Worsening AF” was defined as symptomatic events severe enough to warrant hospitalization for at least 24 hours and change in heart failure therapy.

DATA ON FILE.³

HAZARD RATIO = 0.69 (CI: 0.51-0.93)

TIKOSYN EVENTS = 73

PLACEBO EVENTS = 102

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

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PROARRHYTHMIAS

As with survival, the incidence and discontinuations due to proarrhythmias, particularly TdP, were evaluated in the 3 primary study populations representing patients with a wide range of SHD. The SVA population had a moderate amount of SHD; the DIAMOND studies and the DIAMOND AF population represent a group with a significant amount of SHD.

TdP

TdP is the only arrhythmia that showed a dose-response relationship to TIKOSYN treatment. It did not occur in placebo-treated patients.

The occurrence of TdP decreased markedly after institution of the TIKOSYN dosing regimen based on renal function. Because a number of patients assigned to TIKOSYN were entered prior to dose adjustment based on $\text{Cl}_{\text{cr}}$, there was an opportunity to observe the importance of introducing the algorithm in these trials (Table II).

The overall rate of TdP in the SVA population for all doses was 0.8% (11/1346 patients). The occurrence of TdP in this population increased with TIKOSYN dose and was 0.9% (6/703) for patients treated with > 250 to 500 mcg BID according to the recommended dosing regimen. Overall, 0.7% (11/1346) of the patients in the SVA population discontinued treatment in the hospital because of the development of TdP.
### TABLE II Effect of Tikosyn Dosing Adjustment for CL\textsubscript{CR} on the Rate of TdP

<table>
<thead>
<tr>
<th>Population</th>
<th>TOTAL</th>
<th>BEFORE</th>
<th>AFTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVA*</td>
<td>11/1346 (0.8%)</td>
<td>6/193 (3.1%)</td>
<td>5/1153 (0.4%)</td>
</tr>
<tr>
<td>DIAMOND CHF</td>
<td>25/762 (3.3%)</td>
<td>7/148 (4.7%)</td>
<td>18/614 (2.9%)</td>
</tr>
<tr>
<td>DIAMOND MI</td>
<td>7/749 (0.9%)</td>
<td>3/101 (3.0%)</td>
<td>4/648 (0.6%)</td>
</tr>
<tr>
<td>DIAMOND AF</td>
<td>4/249 (1.6%)</td>
<td>0/43</td>
<td>4/206 (19%)</td>
</tr>
</tbody>
</table>

**DATA ON FILE.**

*Please note that doses up to 750 mcg are included in this analysis.

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. Tikosyn is available only to hospitals and prescribers who have received appropriate Tikosyn dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

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IMPACT OF DOSE REDUCTION

The low TdP rate seen in the clinical trials and the neutral effect of TIKOSYN on mortality may in part be a result of the dosing algorithm. A large number of patients had their dose reduced or discontinued as a result of the algorithm. In the SVA program 239 patients (17.8%) had dose adjusted for renal function and an additional 105 patients (7.8%) for excessive QTc prolongation. In addition, TIKOSYN was discontinued in 0.7% for TdP and in 2.7% for excessive QTc prolongation. Thus, approximately 30% of patients had a dose reduction or discontinuation during in-hospital initiation.

In the DIAMOND population, 47% (CHF) and 45% (MI) of patients on TIKOSYN had their dose adjusted for CLcr. Dose reductions for increased QT interval or QTc occurred in 5% and 7% of DIAMOND CHF and MI patients, respectively. Increased QT interval or QTc (> 550 msec or > 20% increase from baseline) resulted in discontinuation of 1.8% of patients in DIAMOND CHF and 2.5% of patients in DIAMOND MI. Thus, nearly 50% of patients randomized for TIKOSYN in the DIAMOND trials had their dosage either down titrated or discontinued as a result of the drug initiation or dosing principles.

As mentioned above, TIKOSYN must be initiated in a hospital setting. While the rate of TdP can be reduced by adjusting dosage based on CLcr and QTc response, a small incidence of TdP does remain. The majority of TdP reported in the clinical program occurred within the first 3 days (Table 12). Therefore, hospitalization should allow prompt identification and treatment of TdP, should it occur.

SERIOUS ARRHYTHMIAS

Table 12 shows the frequency by randomized dose of serious arrhythmias reported as adverse events in patients with SVAs.

In addition, various forms of conduction disturbances (AV block, bundle branch block, heart block) were observed. Rates were similar to placebo and no dose response was observed.
SUMMARY

Adjustment of TIKOSYN dosing according to renal function resulted in substantial reductions in the incidence of TdP in patients with a wide range of SHD. In addition, the combination of in-hospital initiation of TIKOSYN therapy with ECG monitoring permitted further dose adjustments on the basis of QT/QTc response and identification of patients who were not appropriate for TIKOSYN therapy. Therefore, when one considers the safety data presented, one must remember that these results were obtained using the proposed dosing strategy (see Fig 23).

The incidence of TdP was related to the extent of SHD, with patients in the DIAMOND trials having a higher rate than patients in the SVA trials.

### TABLE 12. INCIDENCE OF SERIOUS ARRHYTHMIAS IN PATIENTS WITH SVAs

<table>
<thead>
<tr>
<th>Arrhythmia event</th>
<th>TIKOSYN DOSAGE</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 250 mcg</td>
<td>250 mcg</td>
</tr>
<tr>
<td></td>
<td>(BID) (n=217)</td>
<td>(BID) (n=388)</td>
</tr>
<tr>
<td>Ventricular arrhythmias*†</td>
<td>3.7%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>0</td>
<td>0.3%</td>
</tr>
<tr>
<td>Ventricular tachycardia†</td>
<td>3.7%</td>
<td>2.6%</td>
</tr>
<tr>
<td>TdP</td>
<td>0</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

*Patients with more than 1 arrhythmia are counted only once in this category.
†Ventricular arrhythmias and ventricular tachycardia include all cases of TdP.
Data on file. 3

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

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There were no cases of TdP in patients receiving a placebo. TdP occurred most often during the first 3 days of treatment, and was self-terminating in 27.3% (3/11) of cases. Despite these careful measures, TdP did occur in patients receiving TIKOSYN. The fact that most TdP with TIKOSYN occurred during the first 3 days of treatment is important, since that is when patients were hospitalized and such events could be most readily identified, treated, and TIKOSYN discontinued in these patients (in all patients with TdP). A small incidence of TdP remained following hospitalization.

**OTHER CLINICAL ADVERSE EVENTS**

The TIKOSYN clinical program included approximately 8600 patients in 130 clinical studies of normal volunteers and patients with supraventricular and ventricular arrhythmias. Adverse events were assessed in 5194 patients, including 2 large-scale placebo-controlled mortality trials (DIAMOND CHF and DIAMOND MI), in which 1511 patients received TIKOSYN for up to 3 years.

In studies of patients with SVAs, 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 TIKOSYN groups were discontinued from clinical trials because of adverse events compared with 8.0% in the placebo groups. The most frequent reason for discontinuation (> 1%) was ventricular tachycardia (2.0% on TIKOSYN).

Table 13 presents other adverse events reported with a frequency > 2% on TIKOSYN than on placebo in the studies of patients with SVAs.

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

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

### TABLE 13. FREQUENCY OF ADVERSE EVENTS OCCURRING AT >2% ON TIKOSYN AND NUMERICALLY MORE OFTEN ON TIKOSYN THAN PLACEBO IN THE SVA POPULATION

<table>
<thead>
<tr>
<th>ADVERSE EVENTS</th>
<th>TIKOSYN (%)</th>
<th>PLACEBO (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Chest pain</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Back pain</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Procedure (medical/surgical/health service)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

DATA ON FILE.³

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

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The incidences of clinically significant laboratory test abnormalities in patients with SVAs were similar for patients on TIKOSYN and those on placebo. No clinically relevant effects were noted in serum alkaline phosphatase, serum gamma-glutamyl transferase (GGT), lactic dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (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 postinfarction and heart failure patient population were generally similar to those seen in the SVA groups.

OVERDOSAGE

There is no antidote for TIKOSYN; treatment of overdose should therefore be symptomatic and supportive. The most prominent manifestation of overdose is likely to be excessive prolongation to 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 TdP 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 TdP. 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-dependant manner. Magnesium sulfate, administered prophylactically either intravenously or orally in a dog model, was effective in the prevention of dofetilide-induced TdP ventricular tachycardia. Similarly, in man, intravenous magnesium sulfate may terminate TdP, irrespective of cause.

TIKOSYN overdose was rare in clinical studies; there were 2 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 2 capsules of 500-mcg doses 1 hour apart and experienced ventricular fibrillation and cardiac arrest 2 hours after the second dose.

In the SVA population only 38 patients received dosage greater than 500 mcg BID, all of whom received 750 mcg BID irrespective of Clcr. In this small patient population, the incidence of TdP was 10.5% (4/38 patients), and the incidence of new ventricular fibrillation was 2.6% (1/38 patients).

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SUMMARY

The results summarized in this section support the positive safety profile of TIKOSYN with respect to survival, proarrhythmic events, clinical adverse events, and clinical laboratory abnormalities in patients with widely varying degrees of SHD. There were no adverse effects on survival in the populations presented, even in patients with severely compromised LV function. The safety record of TIKOSYN has resulted, at least in part, from a dosing strategy (Fig 23) that includes initiation of treatment in the hospital with ECG monitoring, predose adjustment based on renal function, and postdose adjustment based on QT/QTc response. Initiation of therapy in the hospital is important for implementing the dosing algorithm and identifying and managing proarrhythmic events that may occur with TIKOSYN therapy. Because the majority of such events noted in controlled clinical trials occurred during the first 3 days of treatment, hospitalization allows prompt identification and treatment of TdP should it occur. A small number of incidences of TdP remained following hospitalization. Dose adjustment based on renal function helps ensure achievement of appropriate plasma levels of dofetilide; dosing adjustment based on calculated CLcr in controlled clinical trials has been shown to reduce the occurrence of TdP in patients with SVAs as well as in those with significant SHD. The effect of adjusting the dose for renal function can be seen in Table II. Postdose adjustment on the basis of QT/QTc permits correction for the pharmacodynamic effect of therapy in patients whose response is not completely predicted by assessment of renal function.

It is important to fully follow all 3 parts of the TIKOSYN dosing strategy, as detailed in the next section. Careful in-hospital initiation of therapy and establishing appropriate TIKOSYN dosing on the basis of renal function and QT/QTc are some important reasons for the neutral effects of TIKOSYN on mortality in patients with a wide range of severity of SHD.

FIGURE 23. DOSING INITIATION STRATEGY FOR TIKOSYN

<table>
<thead>
<tr>
<th>HOSPITALIZATION AND ECG MONITORING FOR THERAPY INITIATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓</td>
</tr>
<tr>
<td>PREDOSE ADJUSTMENT FOR RENAL FUNCTION</td>
</tr>
<tr>
<td>↓</td>
</tr>
<tr>
<td>POSTDOSE ADJUSTMENT FOR QT/QTc RESPONSE</td>
</tr>
</tbody>
</table>

DATA ON FILE.3

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

Please see full prescribing information and patient information for TIKOSYN® (dofetilide) capsules in back cover pocket.
Therapy with TIKOSYN must be initiated (and, if necessary, re-initiated) in a setting that provides continuous ECG monitoring and in the presence of personnel trained in the management of serious ventricular arrhythmias. Patients should continue to be monitored in this way for a minimum of 3 days or a minimum of 12 hours following electrical or pharmacologic conversion to NSR, whichever period is longer.

The dose of TIKOSYN must be individualized according to CLcr and QTc. QT interval should be used if the heart rate is < 60 beats per minute. There are no data on use of TIKOSYN when the heart rate is < 50 beats per minute. The usual recommended dosage of TIKOSYN is 500 mcg BID, as modified by the dosing algorithm. For consideration of a lower dosage, see Special Considerations.

Serum potassium should be maintained within the normal range before TIKOSYN treatment is initiated and should be maintained within the normal range while the patient remains on TIKOSYN therapy (see WARNINGS, Hypokalemia and Potassium-Depleting Diuretics). In clinical trials, potassium levels were generally maintained above 3.6 to 4.0 mEq/L.

Patients with AF should be anticoagulated according to usual medical practice prior to electrical or pharmacologic cardioversion. Anticoagulant therapy may be continued after cardioversion according to usual medical practice for the treatment of people with AF. Hypokalemia should be corrected before initiation of TIKOSYN therapy (see WARNINGS, Ventricular Arrhythmia). Patients to be discharged on TIKOSYN therapy from an inpatient setting as described above must have an adequate supply of TIKOSYN, at the patient's individualized dose, to allow uninterrupted dosing until the patient receives the first outpatient supply. (see DOSAGE AND ADMINISTRATION)

TIKOSYN is distributed only to those hospitals and other appropriate institutions confirmed to have received applicable dosing and treatment initiation education programs. Inpatient and subsequent outpatient discharge and refill prescriptions are filled only on confirmation that the prescribing physician has received applicable dosing and treatment initiation education programs. For this purpose, a list for use by pharmacists is maintained containing hospitals and physicians who have fulfilled one of the education programs.

The risk of TdP was reduced by following the instructions for individualized dose initiation. Nonetheless, a risk of TdP remained during hospital initiation and following discharge.
INSTRUCTIONS FOR INDIVIDUALIZED DOSE INITIATION

INITIATION OF TIKOSYN THERAPY

Step 1

Electrocardiographic assessment: Prior to administration of the first dose, the QTc must be determined using an average of 5 to 10 beats. If the QTc is greater than 440 msec (500 msec in patients with ventricular conduction abnormalities), TIKOSYN is contraindicated. If heart rate is less than 60 beats per minute, QT interval should be used. Patients with heart rates less than 50 beats per minute have not been studied.

Step 2

CL cr must be calculated using the following formula:

\[
CL_{cr} \text{ (male)} = \frac{(140-\text{age}) \times \text{actual body weight in kg}}{72 \times \text{serum creatinine (mg/dL)}}
\]

\[
CL_{cr} \text{ (female)} = \frac{(140-\text{age}) \times \text{actual body weight in kg} \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}
\]

When serum creatinine is given in \(\mu\) mol/L, divide the value by 88.4 (1 mg/dL = 88.4 \(\mu\) mol/L).

Step 3

Starting dose: The starting dose of TIKOSYN is determined as follows:

<table>
<thead>
<tr>
<th>CALCULATED CL_{CR}</th>
<th>TIKOSYN DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60 mL/min</td>
<td>500 mcg BID</td>
</tr>
<tr>
<td>40-60 mL/min</td>
<td>250 mcg BID</td>
</tr>
<tr>
<td>20-&lt; 40 mL/min</td>
<td>125 mcg BID</td>
</tr>
<tr>
<td>&lt; 20 mL/min</td>
<td>TIKOSYN is contraindicated in these patients</td>
</tr>
</tbody>
</table>

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

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Step 4
- Administer the adjusted TIKOSYN dose and begin continuous ECG monitoring.

Step 5
- At 2 to 3 hours after administering the first dose of TIKOSYN, determine the QTc. If the QTc has increased by greater than 15% compared with baseline established in Step 1
  - or
if the QTc is greater than 500 msec (550 msec in patients with ventricular conduction abnormalities), subsequent dosing should be adjusted as follows:

<table>
<thead>
<tr>
<th>If the Starting Dosage Based on Calculated CLcr Is:</th>
<th>Then the Adjusted Dosage (for QTc Prolongation) Is:</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 mcg BID</td>
<td>250 mcg BID</td>
</tr>
<tr>
<td>250 mcg BID</td>
<td>125 mcg BID</td>
</tr>
<tr>
<td>125 mcg BID</td>
<td>125 mcg QD</td>
</tr>
</tbody>
</table>

Step 6
- At 2 to 3 hours after each subsequent dose of TIKOSYN, determine the QTc (for in-hospital doses 2 through 5). No further downtitration of TIKOSYN based on QTc is recommended.

  NOTE: If at any time after the second dose of TIKOSYN is given, the QTc is greater than 500 msec (550 msec in patients with ventricular conduction abnormalities), TIKOSYN should be discontinued.

Step 7
- Patients are to be continuously monitored by ECG for a minimum of 3 days, or for a minimum of 12 hours after electrical or pharmacologic conversion to NSR, whichever is greater.

The steps described above are summarized in Figure 24.
FIGURE 24. TIKOSYN DOSING ALGORITHM

PLACE PATIENT ON TELEMETRY

Check Baseline QTc
If QTc >440 ms ec, DO NOT use TIKOSYN
If QTc ≤440 ms ec, proceed

Calculate CLCR
MALE: CLCR = (140-AGE) X ACTUAL BODY WEIGHT IN KG
72 X SERUM CREATININE IN MG/DL
FEMALE: CLCR = 0.85 X MALE

If CLCR is <20 mL/min, TIKOSYN is CONTRAINDICATED

If CLCR is >60 mL/min, Give 500 mCG TIKOSYN bid
If CLCR is 40-60 mL/min, Give 250 mCG TIKOSYN bid
If CLCR is 20-<40 mL/min, Give 125 mCG TIKOSYN bid

POSTDOSE ADJUSTMENT: 2-3 HOURS AFTER FIRST DOSE, CHECK QTc

(First dose only) If increase in QTc IS <5%
Continue current dose

(First dose only) If increase in QTc IS >5% OR
>500 MSEC, DECREASE DOSE (SEE TEXT)

If at any time after the second dose, QTc INCREASES >500 MSEC,
TIKOSYN SHOULD BE DISCONTINUED

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. For detailed instructions regarding dose
selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is
available only to hospitals and prescribers who have
received appropriate TIKOSYN dosing and treatment-
initiation education, see DOSAGE AND ADMINISTRATION.

Please see full prescribing information and patient
information for TIKOSYN® (dofetilide) capsules in back
cover pocket.
MAINTENANCE OF TIKOSYN THERAPY

Renal function and QTc should be re-evaluated every 3 months or as medically warranted. If QTc exceeds 500 msec (550 msec in patients with ventricular conduction abnormalities), TIKOSYN therapy should be discontinued and patients should be carefully monitored until QTc returns to baseline levels. If renal function deteriorates, adjust dose as described in Initiation of TIKOSYN Therapy, Step 3.

SPECIAL CONSIDERATIONS

Consideration of a Dose Lower Than That Determined by the Algorithm

The dosing algorithm shown on Figure 24 should be used to determine the individualized dose of TIKOSYN. In clinical trials, the highest dosage of TIKOSYN (500 mcg BID) as modified by the dosing algorithm led to greater effectiveness than lower dosages of 125 mcg BID or 250 mcg BID as modified by the dosing algorithm. The risk of TdP, however, is related to dose as well as to patient characteristics.(see WARNINGS). Physicians, in consultation with their patients, may therefore, in some cases, choose doses lower than determined by the algorithm. It is critically important that if at any time this lower dose is increased, the patient needs to be rehospitalized for 3 days. Previous toleration of higher dosages does not eliminate the need for rehospitalization.

The maximum recommended dosage in patients with a calculated Clcr > 60 mL/min is 500 mcg BID; dosage greater than 500 mcg BID have been associated with an increased incidence of TdP.

A patient who misses a dose should NOT double the next dose. The next dose should be taken at the usual time.

Cardioversion: If patients do not convert to NSR within 24 hours of initiation of TIKOSYN therapy, electrical conversion should be considered. Patients continuing on TIKOSYN after successful electrical cardioversion should continue to be monitored by electrocardiography for 12 hours postcardioversion or a minimum of 3 days after initiation of TIKOSYN therapy, whichever is greater.

SWITCHING TO TIKOSYN FROM CLASS I OR OTHER CLASS III ANTIARRHYTHMIC THERAPY

Before initiating TIKOSYN therapy, previous antiarrhythmic therapy should be withdrawn under careful monitoring for a minimum of 3 plasma half-lives. Because of the unpredictable pharmacokinetics of amiodarone, TIKOSYN should not be initiated following amiodarone therapy until amiodarone plasma levels are below 0.3 mcg/mL or until amiodarone has been withdrawn for at least 3 months.

STOPPING TIKOSYN PRIOR TO ADMINISTRATION OF POTENTIALLY INTERACTING DRUGS

If TIKOSYN needs to be discontinued to allow dosing of other potentially interacting drugs(s), a washout period of at least 2 days should be allowed before starting the other drug(s).
**HOW SUPPLIED**

TIKOSYN is distributed to those hospitals and other appropriate institutions confirmed to have received an applicable dosing and treatment initiation education program. Inpatient and subsequent outpatient discharge and refill prescriptions are filled only upon confirmation that the prescribing physician has received an applicable dosing and initiation education program. For this purpose, a list for use by pharmacists is maintained containing hospitals and physicians who have received one of the education programs.

<table>
<thead>
<tr>
<th>125 MCG (0.125 MG)</th>
<th>250 MCG (0.25 MG)</th>
<th>500 MCG (0.5 MG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obverse</td>
<td>TKN 125</td>
<td>TKN 250</td>
</tr>
<tr>
<td>Reverse</td>
<td>PFIZER</td>
<td>PFIZER</td>
</tr>
<tr>
<td>Bottle of 14</td>
<td>0069-5800-61</td>
<td>0069-5810-61</td>
</tr>
<tr>
<td>Bottle of 60</td>
<td>0069-5800-60</td>
<td>0069-5810-60</td>
</tr>
<tr>
<td>Unit dose/40</td>
<td>0069-5800-43</td>
<td>0069-5810-43</td>
</tr>
</tbody>
</table>

*STORE AT CONTROLLED ROOM TEMPERATURE, 15°C TO 30°C (59°F TO 86°F).*

*PROTECT FROM MOISTURE AND HUMIDITY. DISPENSE IN TIGHT CONTAINERS (USP).*

*Rx ONLY*

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

Please see full prescribing information and patient information for TIKOSYN® (dofetilide) capsules in back cover pocket.
**BOXED WARNING**

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

**INDICATIONS**

- **MAINTENANCE OF NORMAL SINUS RHYTHM (NSR)**
  TIKOSYN is indicated for the maintenance of NSR (delay in time to recurrence of AF/AFl) in patients with AF/AFl of greater than 1 week's duration who have been converted to NSR. Because TIKOSYN can cause life-threatening ventricular arrhythmias, it should be reserved for patients in whom AF/AFl is highly symptomatic.

  In general, antiarrhythmic therapy for AF/AFl aims to prolong the time in NSR. Recurrence is expected in some patients.

- **CONVERSION OF ATRIAL FIBRILLATION/ATRIAL FLUTTER (AF/AFL)**
  TIKOSYN is indicated for the conversion of AF and AFl to NSR. TIKOSYN has not been shown to be effective in patients with paroxysmal AF.

**CONTRAINDICATIONS**

- TIKOSYN is contraindicated in patients with:
  - Congenital or acquired long QT syndromes
  - A baseline QT interval or QTc > 440 msec (500 msec in patients with ventricular conduction abnormalities)
  - Severe renal impairment (Clcr < 20 mL/min)
  - A known hypersensitivity to the drug

- The concomitant use of the following drugs with TIKOSYN is contraindicated:
  - Verapamil
  - Hydrochlorothiazide (alone or in combinations such as with triamterene)

- The following cation transport system inhibitors:
  - Cimetidine
  - Trimethoprim (alone or in combination with sulfamethoxazole)
  - Ketoconazole
  as each of these drugs causes 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.
**WARNINGS**

Ventricular Arrhythmia: TIKOSYN can cause serious ventricular arrhythmias, primarily 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 CL cr or certain TIKOSYN drug interactions will increase dofetilide plasma concentration. The risk of TdP can be reduced by controlling the plasma concentration through adjustment of the initial TIKOSYN dose according to CL cr and by monitoring the ECG for excessive increases in the QT interval.

Treatment with TIKOSYN must, therefore, be started only in patients placed for a minimum of 3 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 CL cr for all patients must precede administration of the first dose of TIKOSYN. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION.

**PHARMACOLOGY: HEMODYNAMIC EFFECTS**

- TIKOSYN has no negative inotropic effects.
- TIKOSYN has no effect on the following:
  - Cardiac output
  - Cardiac index
  - Stroke volume index
  - Systemic vascular resistance

**PHARMACOLOGY: (CONT)**

- In the overall clinical program, TIKOSYN did not affect blood pressure: heart rate was decreased by 4 to 6 beats per minute.

**PHARMACOKINETICS**

TKOSYN has a terminal half-life (t1/2) of approximately 10 hours, which permits twice-daily dosing.

Renal excretion of dofetilide accounts for 80% of its elimination. Therefore, initial dosing must be adjusted based on the calculated CL cr.

TKOSYN is metabolized to a small extent by the CYP3A4 isoenzyme of the cytochrome P450 system. Therefore, inhibitors of the CYP3A4 isoenzyme could increase systemic dofetilide exposure.

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

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The relationship between plasma levels of TIKOSYN and the change from baseline in QTc is predictable and linear.

At the recommended dosage of 500 mcg BID, TIKOSYN converted 30% of patients to NSR versus 1% conversion with placebo.

Of patients who converted pharmacologically, approximately 70% converted within 24 to 36 hours.

The point estimates of the probabilities of remaining in NSR at 12 months were 66% TIKOSYN 500 mcg BID, and 21% on placebo.

Another way to look at the treatment results with TIKOSYN is to look at the number of patients whose therapy was not discontinued for relapse to AF/AFI or other reasons. At 6 months, 57% of patients treated with TIKOSYN 500 mcg BID were still on TIKOSYN and in NSR versus 22% on placebo. At 12 months, 49% of patients on TIKOSYN 500 mcg BID were still on TIKOSYN and in NSR versus 16% on placebo. The arrhythmia-free interval on TIKOSYN was >365 days versus 34 days with placebo ($P<.001$).

Efficacy results for TIKOSYN 250 mcg BID were the following: TIKOSYN converted 10% and 11% of patients to NSR versus 1% with placebo; at 12 months, the probabilities of remaining in NSR were 37% and 51% with TIKOSYN, compared with 25% and 21% with placebo; at 12 months, 26% and 42% of patients were still in NSR and on TIKOSYN, compared with 22% and 16% on placebo; the arrhythmia-free interval with TIKOSYN was 179 to >365 days versus 34 days with placebo.

The safety of TIKOSYN was evaluated in 3 ways: by looking at the effect of TIKOSYN on mortality, the incidence of TdP in the SVA population, and the rate of nuisance side effects.

The results of the 2 large-scale (n=3028) long-term (up to 3-year follow-up) mortality studies DIAMOND CHF (NYHA class III-IV) and DIAMOND MI (median 3 days post-MI) indicated that TIKOSYN produced no excess mortality or morbidity in patients with significant SHD when initiated in-hospital and administered according to renal function and QTc response to therapy. $Q_{cr}$ was calculated using a modified Cockcroft-Gault formula.
A retrospective analysis of 506 patients with AF to baseline randomized to 250 mcg BID in the 2 DIAMOND trials indicated that treatment with TIKOSYN did not adversely affect mortality in patients with LV dysfunction and AF when the dose of TIKOSYN was adjusted for renal function and QTc response to therapy.

A survival analysis based on data pooled from 10 randomized, placebo-controlled trials in patients with AF/AFl showed no statistically significant differences in survival between patients treated with TIKOSYN and those receiving placebo.

In the SVA population (patients with AF and other SVAs evaluated in 10 double-blind placebo-controlled clinical trials), the overall incidence of TdP for all doses was 0.8%. At the recommended TIKOSYN 500 mcg BID dosage, the frequency of TdP was 0.9% (6/703 patients) when dose was adjusted for renal function and QTc response. As noted earlier, the rate of TdP was reduced when patients were dosed according to their renal function.

The most common side effects with TIKOSYN were headache, chest pain, and dizziness.

The safety record of TIKOSYN has resulted, at least in part, from the following dosing strategy that includes initiation of treatment in the hospital with ECG monitoring, predose adjustment based on renal function, and postdose adjustment based on QT/QTc response.

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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

Please see full prescribing information and patient information for TIKOSYN® (dofetilide) capsules in back cover pocket.
It is important to fully follow all 3 parts of the TIKOSYN dosing initiation strategy. In clinical studies, careful in-hospital initiation of therapy and establishing appropriate TIKOSYN dosing on the basis of renal function and QT/QTc are important reasons for the neutral effects of TIKOSYN on mortality in patients with a wide range of severity of SHD.

**DOSAGE AND ADMINISTRATION**

Before TIKOSYN therapy is initiated, the following important guidelines must be followed (see dosing steps on pages 69 and 70):

Therapy with TIKOSYN must be initiated (and, if necessary, re-initiated) in a setting that provides continuous ECG monitoring and in the presence of personnel trained in the management of serious ventricular arrhythmias. Patients should continue to be monitored in this way for a minimum of 3 days or a minimum of 12 hours following electrical or pharmacologic conversion to NSR, whichever period is longer.

The dose must be individualized based on renal function. Clcr must be calculated based on the Cockroft-Gault formula for all patients, regardless of serum creatinine value, prior to the first dose of TIKOSYN.

The postdose QTc response to therapy must be measured and the dose adjusted according to the dosing algorithm.

QT interval should be used if the heart rate is less than 60 beats per minute. There are no data on the use of TIKOSYN when heart rate is less than 50 beats per minute.

**EDUCATION CONFIRMATION**

If you use this product monograph as your education program:

- Please fill out and submit the confirmation form to finalize your enrollment.

If a confirmation form is needed, please:

- Visit www.TIKOSYN.com
- Or call 1-877-TIKOSYN (1-877-845-6796)
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. For detailed instructions regarding dose selection, see DOSAGE AND ADMINISTRATION. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment-initiation education, see DOSAGE AND ADMINISTRATION.

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