Indication

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

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

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

Boxed Warning

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

- Objectives
- Introduction
- TIKOSYN® (dofetilide) mechanism of action
- Pivotal efficacy data
- Safety/risks
- Pharmacokinetics
- Dosing and administration
- REMS
- Support resources

Boxed Warning

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Selected Safety Information

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 (calculated creatinine clearance <20 mL/min), or known hypersensitivity to TIKOSYN.
Objectives

- Objectives
- Introduction
- TIKOSYN® (dofetilide) mechanism of action
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Please see full Prescribing Information, including Boxed Warning, and Medication Guide on slides 52-81, or visit www.TIKOSYNHCP.com.
Objectives

In this presentation, you will:

• Learn the safety and efficacy data behind TIKOSYN® (dofetilide) and how it can help your highly symptomatic atrial fibrillation/atrial flutter (AF/AFL) patients
• Understand how to initiate and maintain TIKOSYN in your patients, including the Risk Evaluation and Mitigation Strategy (REMS) program

Boxed Warning

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Selected Safety Information

The most common adverse events reported were headache, chest pain, dizziness, respiratory tract infection, dyspnea, and nausea.
Introduction

- Objectives
- Introduction
  - AF
    - Definition
    - Prevalence
    - Risk
    - Classification
  - AFL
  - How TIKOSYN® (dofetilide) can treat highly symptomatic AF/AFL
  - TIKOSYN mechanism of action
  - Pivotal efficacy data
  - Safety/risks
  - Pharmacokinetics
  - Dosing and administration
  - REMS
  - Support resources

Boxed Warning

To minimize the risk of induced arrhythmia, patients initiated on TIKOSYN should be placed for a minimum of 3 days in a facility that can provide calculations of creatinine clearance, continuous electrocardiographic monitoring, and cardiac resuscitation. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment initiation education.
The ACCF/AHA/HRS recommends the following definitions for various types of AF:\(^1\):

- **First-detected**: First documented incident of AF; may be paroxysmal or persistent
- **Recurrent**: 2 or more episodes of AF in a single patient
  - **Paroxysmal**: Self-terminating AF; converts spontaneously to normal sinus rhythm (NSR); usually a subtype of recurrent AF
  - **Persistent**: AF that is sustained beyond 7 days and is capable of being converted to NSR; usually a subtype of recurrent AF
- **Long-standing**: AF lasting longer than 1 year
- **Permanent**: When a persistent AF becomes long-standing, it usually leads to a permanent AF, in which cardioversion to NSR has failed or has not been attempted
- **“Lone AF”**: Generally, applies to patients <60 years of age without clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension


**Selected Safety Information**

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 (calculated creatinine clearance <20 mL/min), or known hypersensitivity to TIKOSYN.
AF is a widely prevalent cardiac arrhythmia \(^1\)

- AF is a supraventricular tachyarrhythmia characterized by the presence of uncoordinated atrial activation and deteriorating atrial mechanical function \(^1\).
- AF typically occurs in the presence of other cardiovascular disease or hypertension \(^1\).
- In 2008, it was estimated that AF affected 2.3 million people in the US \(^2\).
  - By 2020, it is estimated that 3 million people will have AF \(^2\).

Selected Safety Information

TIKOSYN is also contraindicated with verapamil, hydrochlorothiazide (alone or in combination, such as with triamterene), and cation transport system inhibitors such as cimetidine, ketoconazole, trimethoprim (alone or in combination with sulfamethoxazole), prochlorperazine, and megestrol because these drugs may cause an increase in dofetilide plasma concentration.

Estimated overall prevalence in general population 0.4% to 1.0%

Proportion of hospitalizations for cardiac arrhythmias due to AF ≈33%

Incidence of chronic AF per year among patients >80 years of age

- In men 2.0%
- In women 1.5%

• AF prevalence increases with each decade of life (up to 8% in patients aged >80 years)¹


Selected Safety Information
The most common adverse events reported were headache, chest pain, dizziness, respiratory tract infection, dyspnea, and nausea.
Persistent AF is associated with serious risks, such as\textsuperscript{1}:

- **Stroke**
  - The average rate of ischemic stroke among patients with nonvalvular AF is 2 to 7 times higher than in patients without AF
  - In patients with rheumatic heart disease, stroke risk is 17 times higher
- **Congestive heart failure (CHF)**
- **Death**—AF is associated with a 2-fold increase in the mortality rate linked to the severity of underlying heart disease
- **Other embolic events**


**Selected Safety Information**

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 (calculated creatinine clearance <20 mL/min), or known hypersensitivity to TIKOSYN.
AF is commonly associated with AFL, another type of supraventricular tachyarrhythmia\(^1\)

- AFL may arise during treatment with antiarrhythmic agents prescribed to prevent recurrent AF
- AFL is characterized by a sawtooth pattern of regular atrial activation called flutter waves on the electrocardiogram (ECG)
- AFL may degenerate into AF, and AF may convert to AFL. The ECG pattern may fluctuate between AFL and AF, reflecting changing activation of the atria

TIKOSYN\(^\circledR\) (dofetilide) can help in the treatment of both highly symptomatic AF and AFL\(^2\)

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**Boxed Warning**

To minimize the risk of induced arrhythmia, patients initiated on TIKOSYN should be placed for a minimum of 3 days in a facility that can provide calculations of creatinine clearance, continuous electrocardiographic monitoring, and cardiac resuscitation. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment initiation education.
TIKOSYN® (dofetilide) is indicated for the maintenance of NSR* in highly symptomatic patients as well as the conversion of AF/AFL to NSR¹

• TIKOSYN is indicated for the maintenance of normal sinus rhythm (delay in time to recurrence of atrial fibrillation/atrial flutter [AF/AFL]) in patients with atrial fibrillation/atrial flutter of greater than one week duration who have been converted to normal sinus rhythm

• Because TIKOSYN can cause life-threatening ventricular arrhythmias, it should be reserved for patients in whom atrial fibrillation/atrial flutter is highly symptomatic

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

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

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

*Delay in AF/AFL recurrence.

¹ Delay in AF/AFL recurrence.


Boxed Warning

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Please see full Prescribing Information, including Boxed Warning, and Medication Guide on slides 52-81, or visit www.TIKOSYNHCP.com.
TIKOSYN® (dofetilide) is recommended as a first-line therapy option in AF treatment for some patient types.

**Selected Safety Information**

The most common adverse events reported were headache, chest pain, dizziness, respiratory tract infection, dyspnea, and nausea.

**Maintenance of Sinus Rhythm**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO (or minimal) heart disease</td>
<td>Dronedarone, flecainide, propafenone, sotalol</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Substantial LVH</td>
</tr>
<tr>
<td>Coronal artery disease</td>
<td>Heart failure</td>
</tr>
</tbody>
</table>

Among highly symptomatic AF patients with coronary artery disease or heart failure, the 2011 ACCF/AHA/HRS treatment guidelines recommend TIKOSYN as a first-line treatment option.

Within each box, drugs are listed alphabetically and not in order of suggested use. The vertical flow indicates order of preference under each condition. The seriousness of heart disease proceeds from left to right, and selection of therapy in patients with multiple conditions depends on the most serious condition present. LVH indicates left ventricular hypertrophy.

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TIKOSYN® (dofetilide) mechanism of action

- Objectives
- Introduction
- **TIKOSYN mechanism of action**
  - How the mechanism of action of TIKOSYN facilitates the conversion and maintenance of NSR by affecting the:
    - Action potential
    - QT interval
- Pivotal efficacy data
- Safety/risks
- Pharmacokinetics
- Dosing and administration
- REMS
- Support resources

**Boxed Warning**

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

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The selective potassium channel-blocking activity of TIKOSYN® (dofetilide) increases the monophasic action potential duration\(^1\)

**SELECTIVE POTASSIUM CHANNEL BLOCKER**

- TIKOSYN blocks only $I_{Kr}$ with no relevant block of the other repolarizing potassium currents (eg, $I_{Ks}$, $I_{K1}$)
  - Blockage of $I_{Kr}$ is associated with Vaughan Williams Class III antiarrhythmic activity
- At clinically relevant concentrations, TIKOSYN has no effect on sodium channels, adrenergic alpha-receptors, or adrenergic beta-receptors

\(^1\) Tikosyn [prescribing information]. New York, NY: Pfizer Inc; 2011.

**Boxed Warning**

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In electrophysiology studies, TIKOSYN® (dofetilide) was found to stop conditions such as AF/AFL and prevent their recurrence¹

By increasing action potential duration, TIKOSYN¹:

- Increases the QT interval observed on the surface ECG
- Terminates induced reentrant tachyarrhythmias such as AF and AFL and prevents their reinduction


Boxed Warning

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Pivotal efficacy data

- Objectives
- Introduction
- TIKOSYN® (dofetilide) mechanism of action
- Pivotal efficacy data
  - EMERALD: European and Australian Multicenter Evaluative Research on Atrial Fibrillation Dofetilide
  - SAFIRE-D: Symptomatic Atrial Fibrillation Investigative Research on Dofetilide
- Safety/risks
- Pharmacokinetics
- Dosing and administration
- REMS
- Support resources

Boxed Warning

To minimize the risk of induced arrhythmia, patients initiated on TIKOSYN should be placed for a minimum of 3 days in a facility that can provide calculations of creatinine clearance, continuous electrocardiographic monitoring, and cardiac resuscitation. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment initiation education.
EMERALD: European and Australian Multicenter Evaluative Research on Atrial Fibrillation Dofetilide

Study design

• A large-scale, placebo-controlled, randomized, 12-month study of 671 patients with a primary diagnosis of AF/AFL of between 1 week and 2 years duration¹
• Patients were randomized to 1 of 5 treatment groups¹:
  — 500 mcg TIKOSYN® (dofetilide) BID
  — 250 mcg TIKOSYN BID
  — 125 mcg TIKOSYN BID
  — 80 mg sotalol BID
  — Placebo
• Dosage was based on calculated creatinine clearance (CrCl)²
• ECG was monitored for the first 3 days of treatment²
• Primary end points¹,²:
  — Conversion phase: Time to and rate of conversion of AF/AFL to NSR
  — Maintenance phase: Times to first relapse to AF/AFL

SAFIRE-D: Symptomatic Atrial Fibrillation Investigative Research on Dofetilide

Study design\textsuperscript{1,2}

- A placebo-controlled, randomized, 12-month study of 325 patients with a primary diagnosis of AF/AFL of more than 1 week duration\textsuperscript{1,2}
- Most patients had New York Heart Association (NYHA) Class II or III structural heart disease (SHD)
- Patients were randomized to 1 of 4 treatment groups:
  - 500 mcg TIKOSYN\textsuperscript{®} (dofetilide) BID
  - 250 mcg TIKOSYN BID
  - 125 mcg TIKOSYN BID
  - Placebo
- Dosage was:
  - Based on calculated creatinine clearance
  - Adjusted downward after evaluation of QT response to therapy
- ECG was monitored for the first 3 days of treatment, at a minimum
- **Primary end points:**
  - **Conversion phase:** Time to and rate of conversion of AF/AFL to NSR
  - **Maintenance phase:** Times to first relapse to AF/AFL

\textsuperscript{1} Tikosyn [prescribing information]. New York, NY: Pfizer Inc; 2011.
The majority of patients in EMERALD and SAFIRE-D had a primary diagnosis of AF¹

Baseline characteristics of patients in EMERALD and SAFIRE-D

<table>
<thead>
<tr>
<th></th>
<th>EMERALD (N=671)</th>
<th>SAFIRE-D (N=325)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>471 (70.2%)</td>
<td>273 (84.0%)</td>
</tr>
<tr>
<td>Age (mean years)</td>
<td>64</td>
<td>67</td>
</tr>
<tr>
<td>Weight (mean kg)</td>
<td>81</td>
<td>88</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>669 (99.7%)</td>
<td>298 (91.7%)</td>
</tr>
<tr>
<td>Black</td>
<td>0 (0.0%)</td>
<td>18 (5.5%)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (&lt;1.0%)</td>
<td>4 (1.2%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (&lt;1.0%)</td>
<td>5 (1.5%)</td>
</tr>
<tr>
<td>SHD</td>
<td>315 (46.9%)</td>
<td>219 (67.3%)</td>
</tr>
<tr>
<td>NYHA Class I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>359 (53.5%)</td>
<td>89 (27.3%)</td>
</tr>
<tr>
<td>III/IV</td>
<td>273 (40.6%)</td>
<td>209 (64.3%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>315 (46.9%)</td>
<td>186 (57.2%)</td>
</tr>
<tr>
<td>CrCl &lt;20-60 mL/min</td>
<td>135 (20.1%)</td>
<td>111 (34.1%)</td>
</tr>
<tr>
<td>AF</td>
<td>599 (89.3%)</td>
<td>277 (85.2%)</td>
</tr>
<tr>
<td>AFL</td>
<td>69 (10.3%)</td>
<td>48 (14.7%)</td>
</tr>
</tbody>
</table>


Please see full Prescribing Information, including Boxed Warning, and Medication Guide on slides 52-81, or visit www.TIKOSYNHCP.com.
Pharmacological conversion increases with increasing doses of TIKOSYN® (dofetilide)¹

- 70% of the patients who converted pharmacologically achieved NSR within 24 to 36 hours of initiation of therapy¹

*P*=.037 vs placebo; †P=.001 vs placebo; ‡P=.015 vs placebo; §P<.001 vs placebo.

In EMERALD, conversion was defined as maintenance of NSR for at least 1 hour and still in NSR on day 3. In SAFIRE-D, conversion was defined as maintenance of NSR for 24 hours.


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Patients receiving TIKOSYN® (dofetilide) were more likely to remain in NSR at 12 months\textsuperscript{1,2}

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TIKOSYN® (dofetilide) patients were significantly more likely to stay in NSR at 12 months¹

Probability of remaining in NSR

<table>
<thead>
<tr>
<th>Dose</th>
<th>Study</th>
<th>n</th>
<th>6 months</th>
<th>12 months</th>
<th>(P) value vs placebo (at 12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIKOSYN 500 mcg BID</td>
<td>EMERALD</td>
<td>100</td>
<td>71%</td>
<td>66%</td>
<td>.0001</td>
</tr>
<tr>
<td></td>
<td>SAFIRE-D</td>
<td>61</td>
<td>62%</td>
<td>58%</td>
<td>.001</td>
</tr>
<tr>
<td>TIKOSYN 250 mcg BID</td>
<td>EMERALD</td>
<td>118</td>
<td>56%</td>
<td>52%</td>
<td>.0001</td>
</tr>
<tr>
<td></td>
<td>SAFIRE-D</td>
<td>61</td>
<td>50%</td>
<td>37%</td>
<td>.104</td>
</tr>
<tr>
<td>TIKOSYN 125 mcg BID</td>
<td>EMERALD</td>
<td>103</td>
<td>51%</td>
<td>40%</td>
<td>.0048</td>
</tr>
<tr>
<td></td>
<td>SAFIRE-D</td>
<td>60</td>
<td>44%</td>
<td>40%</td>
<td>.208</td>
</tr>
<tr>
<td>Placebo</td>
<td>EMERALD</td>
<td>106</td>
<td>26%</td>
<td>21%</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>SAFIRE-D</td>
<td>68</td>
<td>37%</td>
<td>25%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

• Patients still on treatment and in NSR with TIKOSYN 500 mcg²:
  — At 6 months: 57% (EMERALD); 52% (SAFIRE-D)
  — At 12 months: 49% (EMERALD); 46% (SAFIRE-D)


Boxed Warning

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TIKOSYN® (dofetilide) mechanism of action

Safety/risks

- Objectives
- Introduction
- TIKOSYN® (dofetilide) mechanism of action
- Pivotal efficacy data
- Safety/risks
  - Clinical safety experience with TIKOSYN as demonstrated in large, randomized, multicenter clinical trials
    - DIAMOND-CHF and DIAMOND-MI
    - DIAMOND-AF
  - Torsade de Pointes (TdP) and other ventricular arrhythmias associated with TIKOSYN
  - The most common adverse reactions associated with TIKOSYN
  - TIKOSYN tolerability
  - TIKOSYN contraindications
  - Drugs that interact with TIKOSYN
  - Warnings and precautions associated with TIKOSYN
- Pharmacokinetics
- Dosing and administration
- REMS
- Support resources

Selected Safety Information

TIKOSYN is also contraindicated with verapamil, hydrochlorothiazide (alone or in combination, such as with triamterene), and cation transport system inhibitors such as cimetidine, ketoconazole, trimethoprim (alone or in combination with sulfamethoxazole), prochlorperazine, and megestrol because these drugs may cause an increase in dofetilide plasma concentration.
DIAMOND-CHF and DIAMOND-MI evaluated the effect of TIKOSYN® (dofetilide) on morbidity and mortality in patients with impaired left ventricular function¹

Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND)

- **Study design**
  - 2 separate multicenter, randomized, double-blind, placebo-controlled, parallel-group, 3-year studies on mortality and morbidity¹,²
  - DIAMOND-CHF: 1518 patients with moderate to severe congestive heart failure (60% NYHA Class III or IV)²
  - DIAMOND-MI: 1510 patients with a recent myocardial infarction (MI) (40% NYHA Class III or IV)²
  - End points included all-cause mortality and hospitalization due to worsening CHF¹,³,⁴


**Selected Safety Information**

TIKOSYN can cause serious ventricular arrhythmias, primarily Torsade de Pointes type ventricular tachycardia, a polymorphic ventricular tachycardia associated with QT interval prolongation. QT interval prolongation is directly related to dofetilide plasma concentrations. Factors such as reduced creatinine clearance or certain dofetilide drug interactions will increase dofetilide plasma concentration. The risk of TdP can be reduced by controlling the plasma concentration through adjustment of the initial dofetilide dose according to creatinine clearance and by monitoring the ECG for excessive increases in the QT interval. Calculation of creatinine clearance and QTc for all patients must precede administration of the first dose of TIKOSYN. Renal function and QTc should be re-evaluated every 3 months or as medically warranted.
DIAMOND-CHF and DIAMOND-MI evaluated the effect of TIKOSYN® (dofetilide) on morbidity and mortality in patients with impaired left ventricular function

DIAMOND

• Study design (cont’d)
  — Patients received medication as follows:
    • Patients in NSR: 500 mcg TIKOSYN BID or placebo
    • Patients with reduced CrCl or AF/AFL: 250 mcg TIKOSYN BID or QD or placebo
  — Dosage was:
    • Based on calculated creatinine clearance
    • Adjusted downward after evaluation of QT response to therapy
    • Discontinued if dose reduction was required at lowest possible dose study
  — ECG was monitored for the first 3 days of treatment


Selected Safety Information
The most common adverse events reported were headache, chest pain, dizziness, respiratory tract infection, dyspnea, and nausea.
**Patient demographics**

<table>
<thead>
<tr>
<th></th>
<th>DIAMOND-CHF¹</th>
<th></th>
<th>DIAMOND-MI²</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TIKOSYN (n=762)</td>
<td>PLACEBO (n=756)</td>
<td>TIKOSYN (n=749)</td>
<td>PLACEBO (n=761)</td>
</tr>
<tr>
<td>Male</td>
<td>72%</td>
<td>75%</td>
<td>72%</td>
<td>75%</td>
</tr>
<tr>
<td>Age (mean years)</td>
<td>70</td>
<td>70</td>
<td>68</td>
<td>69</td>
</tr>
<tr>
<td>NYHA Class II</td>
<td>35%</td>
<td>39%</td>
<td>54%</td>
<td>53%</td>
</tr>
<tr>
<td>NYHA Class III</td>
<td>56%</td>
<td>51%</td>
<td>30%</td>
<td>32%</td>
</tr>
<tr>
<td>NYHA Class IV</td>
<td>6%</td>
<td>7%</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>History of MI</td>
<td>51%</td>
<td>52%</td>
<td>36%*</td>
<td>37%*</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>9%</td>
<td>11%</td>
<td>36%</td>
<td>37%</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>72%</td>
<td>76%</td>
<td>59%</td>
<td>57%</td>
</tr>
</tbody>
</table>

*These percentages refer to those patients with a history of MI before their recent MI. All patients in DIAMOND-MI had a recent MI (within 7 days prior to enrollment).
TIKOSYN® (dofetilide) had no significant effect on all-cause mortality in DIAMOND-CHF and DIAMOND-MI\textsuperscript{1,2}

- The probability of survival at 1 year with TIKOSYN was\textsuperscript{3}:
  - DIAMOND-CHF: 73\% (95\% CI: 70\%-76\%)
  - DIAMOND-MI: 79\% (95\% CI: 76\%-82\%)


**Boxed Warning**

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

Please see full Prescribing Information, including Boxed Warning, and Medication Guide on slides 52-81, or visit www.TIKOSYNHCP.com.
DIAMOND-AF studied the safety of TIKOSYN® (dofetilide) in patients with AF¹

- Subpopulation of 506 patients in the 2 DIAMOND studies who had AF at entry to the studies
- **Study design**
  - Patients were randomized to 1 of 2 treatment groups
    - 250 mcg BID (n=249)
    - Placebo (n=257)
  - End points included mortality and time to all-cause hospitalization, and hospitalization for worsening CHF²

**Selected Safety Information**

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 (calculated creatinine clearance <20 mL/min), or known hypersensitivity to TIKOSYN.

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Please see full Prescribing Information, including Boxed Warning, and Medication Guide on slides 52-81, or visit www.TIKOSYNHCP.com.
DIAMOND-AF: TIKOSYN® (dofetilide) improved conversion and maintenance of NSR and showed similar rates of overall survival and hospitalization for worsening CHF with placebo¹

- Hospital readmission rates for any reason were 125/249 or 50% on TIKOSYN and 156/257 or 61% on placebo. Of these, readmission rates for worsening heart failure were 73/249 or 29% on TIKOSYN and 102/257 or 40% for placebo¹


Boxed Warning

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

Please see full Prescribing Information, including Boxed Warning, and Medication Guide on slides 52-81, or visit www.TIKOSYNHCP.com.
In the DIAMOND trials, the incidence of TdP showed a dose-dependent relationship to TIKOSYN® (dofetilide)¹

- Like other Vaughan Williams Class III antiarrhythmic drugs, TIKOSYN may cause ventricular arrhythmias, including TdP
  - TdP occurrence increased with TIKOSYN dose
  - QT interval prolongation is directly related to dofetilide plasma concentration
  - Incidence of TdP decreased after initiation of the TIKOSYN dosing regimen based on renal function


Selected Safety Information
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 (calculated creatinine clearance <20 mL/min), or known hypersensitivity to TIKOSYN.
The introduction of the TIKOSYN® (dofetilide) dosing regimen resulted in a reduction in the incidence of TdP

<table>
<thead>
<tr>
<th>Population</th>
<th>TOTAL</th>
<th>BEFORE</th>
<th>AFTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraventricular arrhythmias (SVAs)</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 (0.0%)</td>
<td>4/206 (1.9%)</td>
</tr>
</tbody>
</table>

• Compliance with the TIKOSYN dosing algorithm has been shown to reduce the risk of TdP


Boxed Warning

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

Please see full Prescribing Information, including Boxed Warning, and Medication Guide on slides 52-81, or visit www.TIKOSYNHCP.com.
Lower doses of TIKOSYN® (dofetilide) are associated with lower rates of dangerous ventricular arrhythmias\(^1\)

<table>
<thead>
<tr>
<th>Arrhythmia event</th>
<th>TIKOSYN DOSAGE</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;250 mcg BID (n=217)</td>
<td>250 mcg BID (n=388)</td>
</tr>
<tr>
<td>Ventricular arrhythmias*(^\d)</td>
<td>3.7%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>0.0%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Ventricular tachycardia(^\d)</td>
<td>3.7%</td>
<td>2.6%</td>
</tr>
<tr>
<td>TdP</td>
<td>0.0%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

- TdP is the most serious side effect associated with TIKOSYN, yet is dose-dependent

*Patients with more than one arrhythmia are counted only once in this category.

\(^1\)Ventricular arrhythmias and ventricular tachycardia include all cases of TdP.


**Boxed Warning**

To minimize the risk of induced arrhythmia, patients initiated on TIKOSYN should be placed for a minimum of 3 days in a facility that can provide calculations of creatinine clearance, continuous electrocardiographic monitoring, and cardiac resuscitation. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment initiation education.
The most frequent adverse events associated with TIKOSYN® (dofetilide) included headache, chest pain, and dizziness¹

Adverse events occurring at >2% with TIKOSYN in patients with SVAs

<table>
<thead>
<tr>
<th>Adverse Event</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/surgery/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>

Selected Safety Information

TIKOSYN is also contraindicated with verapamil, hydrochlorothiazide (alone or in combination, such as with triamterene), and cation transport system inhibitors such as cimetidine, ketoconazole, trimethoprim (alone or in combination with sulfamethoxazole), prochlorperazine, and megestrol because these drugs may cause an increase in dofetilide plasma concentration.

TIKOSYN® (dofetilide) was well-tolerated and was not discontinued significantly more often than placebo\textsuperscript{1}.

Discontinuation rates due to adverse reactions in studies of patients with SVAs in the TIKOSYN clinical program\textsuperscript{1}.

- The most frequent reason for discontinuation (>1%) was ventricular tachycardia (2.0% on TIKOSYN vs 1.3% on placebo)\textsuperscript{1}.

Please see full Prescribing Information, including Boxed Warning, and Medication Guide on slides 52-81, or visit www.TIKOSYNHCP.com.

\textsuperscript{1} Tikosyn [prescribing information]. New York, NY: Pfizer Inc; 2011.
TIKOSYN® (dofetilide) use should be avoided in patients who are contraindicated¹

- TIKOSYN is contraindicated in patients with congenital or acquired long QT syndromes
  - TIKOSYN should not be used in patients with a baseline QT interval or QTc >440 msec (500 msec in patients with ventricular conduction abnormalities)
- TIKOSYN is also contraindicated in patients with severe renal impairment (calculated creatinine clearance <20 mL/min)
- The concomitant use of verapamil or the cation transport system inhibitors cimetidine, trimethoprim (alone or in combination with sulfamethoxazole), or ketoconazole with TIKOSYN is contraindicated, as each of these drugs cause a substantial increase in dofetilide plasma concentrations
  - Other known inhibitors of the renal cation transport system such as prochlorperazine and megestrol should not be used in patients on TIKOSYN
- The concomitant use of hydrochlorothiazide (alone or in combinations such as with triamterene) with TIKOSYN is contraindicated because this has been shown to significantly increase dofetilide plasma concentrations and QT interval prolongation
- TIKOSYN is also contraindicated in patients with a known hypersensitivity to the drug

Careful attention should be paid to the interactions of TIKOSYN® (dofetilide) in order to ensure its safe use

<table>
<thead>
<tr>
<th>TIKOSYN should not be taken with:</th>
<th>The use of TIKOSYN with drugs that prolong the QT interval has not been studied and is not recommended:</th>
<th>TIKOSYN should be cautiously co-administered with CYP3A4 isoenzyme inhibitors:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Verapamil</td>
<td>• Phenothiazines</td>
<td>• Macrolide antibiotics</td>
</tr>
<tr>
<td>• Hydrochlorothiazide (alone or in combinations such as with triamterene)</td>
<td>• Cisapride</td>
<td>• Azole antifungal agents</td>
</tr>
<tr>
<td>• Cimetidine</td>
<td>• Bepridil</td>
<td>• Protease inhibitors</td>
</tr>
<tr>
<td>• Ketoconazole</td>
<td>• Tricyclic antidepressants</td>
<td>• Serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>• Trimethoprim (alone or in combination with sulfamethoxazole)</td>
<td>• Certain oral macrolides</td>
<td>• Amiodarone</td>
</tr>
<tr>
<td>• Prochlorperazine</td>
<td>• Certain fluoroquinolones</td>
<td>• Cannabinoids</td>
</tr>
<tr>
<td>• Megestrol</td>
<td></td>
<td>• Diltiazem</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Grapefruit juice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Nefazodone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Norfloxacin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Quinine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Zafirlukast</td>
</tr>
</tbody>
</table>

TIKOSYN does not inhibit the CYP34A or cytochrome P450 isoenzymes

Please see full Prescribing Information, including Boxed Warning, and Medication Guide on slides 52-81, or visit www.TIKOSYNHCP.com.

Boxed Warning associated with TIKOSYN®
(dofetilide)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. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment initiation education.

Ventricular arrhythmia

• TIKOSYN can cause serious ventricular arrhythmias, primarily TdP type ventricular tachycardia
• QT interval prolongation is directly related to TIKOSYN plasma concentration. Factors such as reduced CrCl or certain TIKOSYN drug interactions will increase TIKOSYN plasma concentration
• The risk of TdP can be reduced by controlling the plasma concentration through adjustment of the initial TIKOSYN dose according to creatinine clearance and by monitoring the ECG for excessive increases in the QT interval
• Calculation of the CrCl for all patients must precede administration of the first dose of TIKOSYN
• The QT interval increases linearly with increasing TIKOSYN dose

Please see full Prescribing Information, including Boxed Warning, and Medication Guide on slides 52-81, or visit www.TIKOSYHNHC.com.

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
Renal impairment

- The overall systemic clearance of dofetilide is decreased and plasma concentration increased with decreasing creatinine clearance. The dose of TIKOSYN must be adjusted based on creatinine clearance.

Hepatic impairment

- After adjustment for creatinine clearance, no additional dose adjustment is required for patients with mild or moderate hepatic impairment.
To minimize the risk of induced arrhythmia, patients initiated on TIKOSYN should be placed for a minimum of 3 days in a facility that can provide calculations of creatinine clearance, continuous electrocardiographic monitoring, and cardiac resuscitation. TIKOSYN is available only to hospitals and prescribers who have received appropriate TIKOSYN dosing and treatment initiation education.
TIKOSYN® (dofetilide) has a short half-life and BID dosing

- TIKOSYN has a terminal half-life of about 10 hours, permitting BID dosing
- Approximately 80% of each dose is excreted by the kidneys
- There is a linear relationship between TIKOSYN plasma levels and the QTc

![Graph showing relationship between TIKOSYN dose, QTc increase, and maintenance of NSR]

Number of patients evaluated for maintenance of NSR: 503 TIKOSYN, 174 placebo.
Number of patients evaluated for QTc change: 478 TIKOSYN, 167 placebo.

In these studies, doses were modified by results of CrCl measurement and in-hospital QTc prolongation.


Please see full Prescribing Information, including Boxed Warning, and Medication Guide on slides 52-81, or visit www.TIKOSYNHCP.com.
Pharmacokinetics in special populations

Renal impairment

- Clearance of dofetilide decreases with decreasing creatinine clearance
- In clinical studies, the half-life of dofetilide is longer in patients with lower creatinine clearances
- Because increase in QT interval and the risk of ventricular arrhythmias are directly related to plasma concentrations of dofetilide, dosage adjustment based on calculated creatinine clearance is critically important
- Patients with severe renal impairment (creatinine clearance <20 mL/min) were not included in clinical or pharmacokinetic studies

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)
- Patients with severe hepatic impairment were not studied

Please see full Prescribing Information, including Boxed Warning, and Medication Guide on slides 52-81, or visit www.TIKOSYNHCP.com.

Pharmacokinetics in special populations

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.

Elderly

- After correction for renal function, clearance of dofetilide is not related to age.

Women

- Women have approximately 12% to 18% lower dofetilide oral clearances than men (14% to 22% greater plasma dofetilide levels), after correction for weight and creatinine clearance.
- In females, as in males, renal function was the single most important factor influencing dofetilide clearance.
Dosing and administration

• Objectives
• Introduction
• TIKOSYN® (dofetilide) mechanism of action
• Pivotal efficacy data
• Safety/risks
• Pharmacokinetics
• **Dosing and administration**
  — How to initiate TIKOSYN safely and effectively
• REMS
• Support resources

**Boxed Warning**

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

Please see full Prescribing Information, including Boxed Warning, and Medication Guide on slides 52-81, or visit www.TIKOSYNHCP.com.
In order to minimize the risk of induced arrhythmia and to safely determine the correct dose, TIKOSYN® (dofetilide) must be administered during a 3-day hospital stay by following this 7-step algorithm¹

Place patient on telemetry

Check baseline QTc
If QTc >440 msec: DO NOT USE TIKOSYN
If QTc ≤440 msec: proceed

Calculate CrCl
Male CrCl = (140-age) x actual body weight in kg
72 x serum creatinine (mg/dl)
Female CrCl = 0.85 x male

If CrCl is <20 mL/min: TIKOSYN is CONTRAINDICATED
If CrCl is >60 mL/min: give 500 mcg TIKOSYN BID
If CrCl is 40–60 mL/min: give 250 mcg TIKOSYN BID
If CrCl is 20–<40 mL/min: give 125 mcg TIKOSYN BID

2-3 hours after dose: check QTc
(First dose only) If increase in QTc is ≤15%; continue current dose
(First dose only) If increase in QTc is >15%, or >500 msec: decrease dose (see above)

If at any time after the second dose QTc increases >500 msec: TIKOSYN should be discontinued

DOSE ADJUSTMENTS
If starting dose is: Adjusted dose is:
500 mcg BID 250 mcg BID
250 mcg BID 125 mcg BID
125 mcg BID 125 mcg QD

Please see full Prescribing Information, including Boxed Warning, and Medication Guide on slides 52-81, or visit www.TIKOSYNHCP.com.

Risk Evaluation and Mitigation Strategy (REMS)

- Objectives
- Introduction
- TIKOSYN® (dofetilide) mechanism of action
- Pivotal efficacy data
- Safety/risks
- Pharmacokinetics
- Dosing and administration
- REMS
  - TIKOSYN overview and REMS
  - How to certify
- Support resources

Boxed Warning

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

TIKOSYN® (dofetilide) REMS helps mitigate the risk of a TIKOSYN-induced arrhythmia

The TIKOSYN REMS protects patients by ensuring that:

• TIKOSYN is:
  — Prescribed only by certified prescribers
  — Dispensed only by retail and institutional pharmacies
  — Dispensed for use only with documentation of safe use conditions

• Healthcare providers are educated about the risks and the need to initiate and re-initiate therapy in a healthcare facility that can provide calculations of CrCl, continuous ECG monitoring, and cardiac resuscitation

• Patients are informed about the serious risks associated with TIKOSYN therapy

Certification to prescribe TIKOSYN® (dofetilide) is quick and easy

After reviewing the following brief materials, healthcare providers can certify by signing and returning the certification form¹

- TIKOSYN Treatment Guidelines
- TIKOSYN Prescribing Information
- TIKOSYN Medication Guide
- Institution Certification Form

To access these materials and become certified to prescribe TIKOSYN, visit www.TIKOSYNREMS.com


Selected Safety Information

TIKOSYN can cause serious ventricular arrhythmias, primarily Torsade de Pointes type ventricular tachycardia, a polymorphic ventricular tachycardia associated with QT interval prolongation. QT interval prolongation is directly related to dofetilide plasma concentrations. Factors such as reduced creatinine clearance or certain dofetilide drug interactions will increase dofetilide plasma concentration. The risk of TdP can be reduced by controlling the plasma concentration through adjustment of the initial dofetilide dose according to creatinine clearance and by monitoring the ECG for excessive increases in the QT interval. Calculation of creatinine clearance and QTc for all patients must precede administration of the first dose of TIKOSYN. Renal function and QTc should be re-evaluated every 3 months or as medically warranted.

Please see full Prescribing Information, including Boxed Warning, and Medication Guide on slides 52-81, or visit www.TIKOSYNHCP.com.
Support resources

- Objectives
- Introduction
- TIKOSYN® (dofetilide) mechanism of action
- Pivotal efficacy data
- Safety/risks
- Pharmacokinetics
- Dosing and administration
- REMS
- Support resources
  - TIKOSYNtogether™
  - PfizerPro
  - TIKOSYN Information Network

Boxed Warning

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

TIKOSYNtogether™

The TIKOSYNtogether Support Program is a simple, easy way to enhance the care you and your team provide your AF/AFL patients. Learn more at:
www.TIKOSYN.com

PfizerPro

PfizerPro is your online resource for all TIKOSYN® (dofetilide) information. Access Pfizer’s HCP TIKOSYN website at:
www.TIKOSYNHCP.com

TIKOSYN Information Network

Trained professionals including pharmacists will be available Monday through Friday to answer any questions about the medication at:
1-877-TIKOSYN
(1-877-845-6796)
Hours of availability: 8 AM ET to 8 PM ET
TIKOSYN®
(dofetilide)
Capsules

To minimize the risk of induced arrhythmias, 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.

DESCRIPTION

TIKOSYN® (dofetilide) is an antiarrhythmic drug with Class III (cardiac action potential duration prolonging) properties. Its empirical formula is C₂₀H₂₂N₂O₂S₂, and it has a molecular weight of 441.6. The structural formula is:

![Structural formula of dofetilide]

The chemical name for dofetilide is:

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 three dosage 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.

CLINICAL PHARMACOLOGY

Mechanism of Action

TIKOSYN (dofetilide) exhibits 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, IKᵣ. At concentrations covering several orders of magnitude, dofetilide blocks only IKᵣ with no relevant block of the other repolarizing potassium currents.

Please see full Prescribing Information, including Boxed Warning, and Medication Guide on slides 52-81, or visit www.TIKOSYNHCP.com.
(e.g., I_{Na}, I_{K}). At clinically relevant concentrations, dofetilide has no effect on sodium channels (associated with Class 1 effect), adrenergic alpha-receptors, or adrenergic beta-receptors.

**Electrophysiology**

TIKOSYN (dofetilide) increases 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 electrophysiology studies. The increase in QT interval observed on the surface ECG is a result of prolongation of both effective and functional refractory periods in the His-Purkinje system and the ventricles.

Dofetilide did not influence cardiac conduction velocity and sinus node function in a variety of studies in patients with or without structural heart disease. This is consistent with a lack of effect of dofetilide on the PK interval and QRS width in patients with pre-existing heart block and/or sick sinus syndrome.

In patients, dofetilide terminates induced re-entrant tachyarrhythmias (e.g. atrial fibrillation/flutter 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, TIKOSYN had no effect on cardiac output, cardiac index, stroke volume index, or systemic vascular resistance in patients with ventricular tachycardia, mild to moderate congestive heart failure or angina, and either normal or low left ventricular ejection fraction. There was no evidence of a negative inotropic effect related to TIKOSYN therapy in patients with atrial fibrillation. There was no increase in heart rate in patients with significant left ventricular dysfunction (see CLINICAL STUDIES, Safety in Patients with Structural Heart Disease, DIAMOND Studies). In the overall clinical program, TIKOSYN did not affect blood pressure. Heart rate was decreased by 4-6 bpm in studies in patients.

**Pharmacokinetics, General**

Absorption and Distribution: The oral bioavailability of dofetilide is >90%, with maximal plasma concentrations occurring at about 2-3 hours in the fasted state. Oral bioavailability is unaffected by food or antacid. The terminal half-life of TIKOSYN is approximately 10 hours; steady state plasma concentrations are attained within 2-3 days, with an accumulation index of 1.5 to 2.0. Plasma concentrations are dose proportional. Plasma protein binding of dofetilide is 60-70%, is independent of plasma concentration, and is unaffected by renal impairment. Volume of distribution is 3 L/kg.

Metabolism and Excretion: Approximately 80% of a single dose of dofetilide is excreted in urine, of which approximately 80% is excreted as unchanged dofetilide with the remaining 20% consisting 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, meperidine, and ketocanazole). In-vitro studies with human liver microsomes show that dofetilide can be metabolized by CYP3A4, but it has a low affinity for this isoenzyme. Metabolites are formed by N-dealkylation and N-
oxidation. There are no quantifiable metabolites circulating in plasma, but 5 metabolites have been identified in urine.

**Pharmacokinetics in Special Populations**

**Renal Impairment:** In volunteers with varying degrees of renal impairment and patients with arrhythmias, the clearance of dofetilide decreases with decreasing creatinine clearance. As a result, and as seen in clinical studies, the half-life of dofetilide is longer in patients with lower creatinine clearances. Because increase in QT interval and the risk of ventricular arrhythmias are directly related to plasma concentrations of dofetilide, dosage adjustment based on calculated creatinine clearance is critically important (see DOSAGE AND ADMINISTRATION). Patients with severe renal impairment (creatinine clearance <20 mL/min) were not included in clinical or pharmacokinetic studies (see CONTRAINDICATIONS).

**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 to age- and weight-matched healthy volunteers. Patients with severe hepatic impairment were not studied.

**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.

**Elderly:** After correction for renal function, clearance of dofetilide is not related to age.

**Women:** A population pharmacokinetic analysis showed that women have approximately 12–18% lower dofetilide oral clearances than men (14–22% greater plasma dofetilide levels), after correction for weight and creatinine clearance. 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.

**Drug-Drug Interactions (see PRECAUTIONS)**

**Dose-Response and Concentration Response for Increase in QT Interval**

Increase in QT interval is directly related to dofetilide dose and plasma concentration. Figure 1 shows that the relationship in normal volunteers between dofetilide plasma concentrations and change in QTc is linear, with a positive slope of approximately 15–25 msec/(ng/mL) after the first dose and approximately 10–15 msec/(ng/mL) at Day 23 (reflecting a steady state of dosing). 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.
Figure 1: Mean QTc-Concentration Relationship in Young Volunteers Over 24 Days

Note: The range of dofetilide plasma concentrations achieved with the 500 mcg BID dose adjusted for creatinine clearance is 1–3.5 ng/mL.

The relationship between dose, efficacy, and the increase in QTc from baseline at steady state for the two randomized, placebo-controlled studies (described further below) is shown in Figure 2. The studies examined the effectiveness of TIKOSYN in conversion to sinus rhythm and maintenance of normal sinus rhythm after conversion in patients with atrial fibrillation/flutter of >1 week duration. As shown, both the probability of a patient’s remaining in sinus rhythm at six 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 creatinine clearance measurement and in-hospital QTc prolongation.

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**CLINICAL STUDIES**

**Chronic Atrial Fibrillation and/or Atrial Flutter**

Two randomized, parallel, double-blind, placebo-controlled, dose-response trials evaluated the ability of TIKOSYN 1) to convert patients with atrial fibrillation or atrial flutter (AF/AFib) of more than 1 week duration to normal sinus rhythm (NSR) and 2) to maintain NSR (delay time to recurrence of AF/AFib) after drug-induced or electrical cardioversion. A total of 996 patients with a one week to two year history of atrial fibrillation/atrial flutter were enrolled. Both studies randomized patients to placebo or to doses of TIKOSYN 125 mg, 250 mg, 500 mg, or in one study a comparator drug, given twice a day (these doses were lowered based on calculated creatinine clearance and, in one of the studies, for QT interval or QTc). All patients were started on therapy in a hospital where their ECG was monitored (see DOSAGE AND ADMINISTRATION).

Patients were excluded from participation if they had had syncope within the past 6 months, AV block greater than first degree, MI or unstable angina within 1 month, cardiac surgery within 2 months, history of QT interval prolongation or polymorphic ventricular tachycardia associated with use of antiarrhythmic drugs, QT interval or QTc >440 msec, serum creatinine >2.5 mg/dL, significant diseases of other organ systems, used cimetidine, or used drugs known to prolong the QT interval.

Both studies enrolled mostly Caucasians (over 90%), males (over 70%), and patients ≥65 years of age (over 50%). Most (≥90%) were NYHA Functional Class I or II. Approximately one-half had structural heart disease (including ischemic heart disease, cardiomyopathies, and valvular disease) and about one-half were hypertensive. A substantial proportion of patients were on
concomitant therapy, including digoxin (over 60%), diuretics (over 20%), and ACE inhibitors (over 30%). About 90% were on anticoagulants.

Acute conversion rates are shown in Table 1 for randomized doses (doses were adjusted for calculated creatinine clearance and, in Study 1, for QT interval or QTc). Of patients who converted pharmacologically, approximately 70% converted within 24-36 hours.

Table 1: Conversion of Atrial Fibrillation/Flutter to Normal Sinus Rhythm

<table>
<thead>
<tr>
<th>Study</th>
<th>125 mg BID</th>
<th>250 mg BID</th>
<th>500 mg BID</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>5/8 (62.5%)</td>
<td>4/8 (50%)</td>
<td>3/8 (37.5%)</td>
<td>1/8 (12.5%)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>3/13 (23%)</td>
<td>1/13 (7.7%)</td>
<td>0/13</td>
<td>0/13</td>
</tr>
</tbody>
</table>

Patients who did not convert to NSR with randomized therapy within 48-72 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 one year unless they experienced a recurrence of atrial fibrillation/atrial flutter or withdrew for other reasons.

Table 2 shows, by randomized dose, the percentage of patients at 6 and 12 months in both studies who remained on treatment in NSR and the percentage of patients who withdrew because of recurrence of AF/AFI or adverse events.

Table 2: Patient Status at 6 and 12 Months Post Randomization

<table>
<thead>
<tr>
<th>Study</th>
<th>Dikosyn Dose</th>
<th>125 mg BID</th>
<th>250 mg BID</th>
<th>500 mg BID</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Randomized</td>
<td>62</td>
<td>61</td>
<td>68</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Achieved NSR</td>
<td>60</td>
<td>61</td>
<td>61</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Still on treatment in NSR</td>
<td>38%</td>
<td>44%</td>
<td>32%</td>
<td>32%</td>
</tr>
<tr>
<td></td>
<td>DEX (in occurrence)</td>
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<td>49%</td>
<td>33%</td>
<td>0.3%</td>
</tr>
<tr>
<td></td>
<td>DEX (for AFI)</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Randomized</td>
<td>62</td>
<td>61</td>
<td>68</td>
<td>64</td>
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<td>DEX (for AFI)</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Note that columns do not add up 100% due to discontinuations for “other” reasons.
Table 3 and Figures 3 and 4 show, by randomized dose, the effectiveness of Tikosyn in maintaining NSR using Kaplan Meier analysis, which shows patients remaining on treatment.

Table 3: P-Values and Median Time (days) to Recurrence of AFAFI

<table>
<thead>
<tr>
<th>Dose</th>
<th>125 mg BID</th>
<th>250 mg BID</th>
<th>500 mg BID</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value vs. placebo</td>
<td>0.21</td>
<td>0.10</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Median time to recurrence (days)</td>
<td>31</td>
<td>170</td>
<td>&gt;365</td>
<td>27</td>
</tr>
</tbody>
</table>

Median time to recurrence of AFAFI could not be estimated accurately for the 250 mg BID treatment group in Study 2 and the 300 mg BID treatment group in Studies 1 and 2 because Tikosyn maintained >90% of patients (55%, 58%, and 68%, respectively) in NSR for the 12 month duration of the studies.

Figure 3: Maintenance of Normal Sinus Rhythm, Tikosyn Regimen vs. Placebo (Study 1)

The point estimates of the probabilities of remaining in NSR at 6 and 12 months were 62% and 58%, respectively, for Tikosyn 500 mg BID, 50% and 37%, respectively, for Tikosyn 250 mg BID; and 37%, and 23%, respectively, for placebo.

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The point estimates of the probabilities of remaining in NSR at 6 and 12 months were 71% and 66%, respectively, for TIKOSYN 500 mcg BID, 56% and 51%, respectively, for TIKOSYN 250 mcg BID, and 26% and 21%, respectively, for placebo.

In both studies, TIKOSYN resulted in a dose-related increase in the number of patients maintained in NSR at all time periods and delayed the time of recurrence of sustained AF. Data pooled from both studies show that there is a positive relationship between the probability of staying in NSR, TIKOSYN dose, and increase in QTc (see Figure 2 in CLINICAL PHARMACOLOGY, Dose-Response and Concentration Response for Increase in QT Interval).

Analysis of pooled data for patients randomized to a TIKOSYN dose of 500 mcg twice daily showed that maintenance of NSR was similar in both males and females, in both patients aged <65 years and patients ≥65 years of age, and in both patients with atrial flutter as a primary diagnosis and those with a primary diagnosis of atrial fibrillation.

During the period of in-hospital initiation of dosing, 23% of patients in Studies 1 and 2 had their dose adjusted downward on the basis of their calculated creatinine clearance, and 3% had their dose down-titrated due to increased QT interval or QTc. Increased QT interval or QTc led to discontinuation of therapy in 3% of patients.

Safety in Patients with Structural Heart Disease: DIAMOND Studies (The Danish Investigations of Arrhythmia and Mortality on Dofetilide)
The two DIAMOND studies were 3-year trials comparing the effects of TIKOSYN and placebo on mortality and morbidity in patients with impaired left ventricular function (ejection fraction ≤ 35%). Patients were treated for at least one year. One study was in patients with moderate to severe (60% NYHA Class III or IV) congestive heart failure (DIAMOND CHF) and the other...
was in patients with recent myocardial infarction (DIAMOND MI) (of whom 40% had NYHA Class III or IV heart failure). Both groups were at relatively high risk of sudden death. The DIAMOND trials were intended to determine whether TIKOSYN could reduce that risk. 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 in patients with structural heart disease, 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 in post-infarction populations. The DIAMOND trials therefore provide evidence of a method of safe use of TIKOSYN in a population susceptible to ventricular arrhythmias. In addition, the subset of patients with AF in the DIAMOND trials provide further evidence of efficacy in a population of patients with structural heart disease accompanying the AF. Note, however, that this AF population was given a lower (250 mcg BID) dose (see CLINICAL STUDIES, DIAMOND Patients with Atrial Fibrillation).

In both DIAMOND studies, patients were randomized to 500 mcg BID of TIKOSYN, but this was reduced to 250 mcg BID if calculated creatinine clearance was 40-60 ml/min, if patients had AF, or if QT interval prolongation (>50 msec or >20% increase from baseline) occurred after dosing. Dose reductions for reduced calculated creatinine clearance occurred in 47% and 45% of DIAMOND CHF and MI patients, respectively. 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 (>50 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.

In the DIAMOND studies, all patients were hospitalized for at least 3 days after treatment was initiated and monitored by telemetry. Patients with QTc greater than 460 msec, second or third degree AV block (unless with pacemaker), resting heart rate <50 bpm, or prior history of polymorphic ventricular tachycardia were excluded.

DIAMOND CHF studied 1518 patients hospitalized with severe CHF who had confirmed impaired left ventricular function (ejection fraction <55%). Patients received a median duration of therapy of greater than one year. There were 311 deaths from all causes in patients randomized to TIKOSYN (n=762) and 317 deaths in patients randomized to placebo (n=756). The probability of survival at one year was 73% (95% CI: 70% - 76%) in the TIKOSYN group and 72% (95% CI: 69% - 75%) in the placebo group. Similar results were seen for cardiac deaths and arrhythmic deaths. Torsade de Pointes occurred in 25/762 patients (3.3%) receiving TIKOSYN. The majority of cases (76%) occurred within the first 3 days of dosing. In all, 425/762 (57%) of patients on TIKOSYN and 459/756 (61%) on placebo required hospitalization. Of these, 229/762 (30%) of patients on TIKOSYN and 290/756 (38%) on placebo required hospitalization because of worsening heart failure.

DIAMOND MI studied 1510 patients hospitalized with recent myocardial infarction (2–7 days) who had confirmed impaired left ventricular function (ejection fraction <55%). Patients received a median duration of therapy of greater than one year. There were 230 deaths in patients randomized to TIKOSYN (n=749) and 243 deaths in patients randomized to placebo (n=761). The probability of survival at one year was 79% (95% CI: 76% - 82%) in the TIKOSYN group and 77% (95% CI: 74% - 80%) in the placebo group. Cardiac and arrhythmic mortality showed a similar result. Torsade de Pointes occurred in 17/749 patients (0.9%) receiving TIKOSYN. Of
these, 4 cases occurred within the first 3 days of dosing and 3 cases occurred between Day 4 and the conclusion of the study. In all, 371/759 (50%) of patients on TIKOSYN and 418/761 (55%) on placebo required hospitalization. Of these, 208/749 (27%) of patients on TIKOSYN and 205/761 (27%) on placebo required hospitalization because of worsening heart failure.

**DIAMOND Patients with Atrial Fibrillation** (the DIAMOND AF subpopulation) There were 506 patients in the two DIAMOND studies who had atrial fibrillation (AF) at entry to the studies (249 randomized to TIKOSYN and 257 randomized to placebo). DIAMOND AF patients randomized to TIKOSYN received 250 mcg BID, 65% of these patients had impaired renal function, so that 250 mcg BID represents the dose 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. Hospital readmission rates for any reason were 125/249 or 50% on TIKOSYN and 150/257 or 61% for placebo. Of these, readmission rates for worsening heart failure were 73/249 or 29% on TIKOSYN and 102/257 or 40% for placebo.

Of the 506 patients in the DIAMOND studies who had atrial fibrillation or flutter at baseline, 12% of patients in the TIKOSYN group and 2% of patients in the placebo group had converted to normal sinus rhythm after one month. In those patients converted to normal sinus rhythm, 79% of the TIKOSYN group and 62% of the placebo group remained in normal sinus rhythm for one year.

In the DIAMOND studies, although Torsade de Pointes occurred more frequently in the TIKOSYN-treated patients (see ADVERSE REACTIONS), TIKOSYN, given with an initial 3-day hospitalization and with dose modified for reduced creatinine clearance and increased QT interval, was not associated with an excess risk of mortality in these populations with structural heart disease in the individual studies or in an analysis of the combined studies. The presence of atrial fibrillation did not affect outcome.

**INDICATIONS AND USAGE**

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

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

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

**Conversion of Atrial Fibrillation/Flutter**

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

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

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

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

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

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

WARNINGS

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

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

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

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

Hypokalemia and Potassium-Depleting Diuretics
Hypokalemia or hypomagnesemia may occur with administration of potassium-depleting diuretics, increasing the potential for Torsade de Pointes. Potassium levels should be within the normal range prior to administration of TIKOSYN and maintained in the normal range during administration of TIKOSYN (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 three half-lives prior to dosing with TIKOSYN. In clinical trials, TIKOSYN was administered to patients previously treated with oral amiodarone only if serum amiodarone levels were below 0.3 mg/L or amiodarone had been withdrawn for at least three months.

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

Hepatic Impairment
After adjustment for creatinine clearance, no additional dose adjustment is required for patients with mild or moderate hepatic impairment. Patients with severe hepatic impairment have not been studied. TIKOSYN should be used with particular caution in these patients.
Cardiac Conduction Disturbances
Animal and human studies have not shown any adverse effects of dofetilide on conduction velocity. No effect on AV nodal conduction following TIKOSYN treatment was noted in normal volunteers and in patients with 1st degree heart block. Patients with sick sinus syndrome or with 2nd or 3rd degree heart block were not included in the Phase 3 clinical trials unless a functioning pacemaker was present. TIKOSYN has been used safely in conjunction with pacemakers (53 patients in DIAMOND studies, 136 in trials in patients with ventricular and supraventricular arrhythmias).

Information for Patients
Please refer patient to the Medication Guide.

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

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

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

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

Drug/Laboratory Test Interactions
None known.
Drug-Drug Interactions

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

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

Ketoconazole: (see WARNINGS, CONTRAINDICATIONS) Concomitant use of ketoconazole is contraindicated. Ketoconazole at 400 mg daily (the maximum approved prescription dose) co-administered with TIKOSYN (500 mcg BID) for 7 days has been shown to increase dofetilide C_{max} by 53% in males and 97% in females, and AUC by 41% in males and 99% in females.

Trimethoprim Alone or in Combination with Sulfamethoxazole: (see WARNINGS, CONTRAINDICATIONS) Concomitant use of trimethoprim alone or in combination with sulfamethoxazole is contraindicated. Trimethoprim 160 mg in combination with 800 mg sulfamethoxazole co-administered BID with TIKOSYN (500 mcg BID) for 4 days has been shown to increase dofetilide AUC by 100% and C_{max} by 92%.

Hydrochlorothiazide (HCTZ) Alone or in Combination with Triamterene: (see CONTRAINDICATIONS) Concomitant use of HCTZ alone or in combination with triamterene is contraindicated. HCTZ 50 mg QD or HCTZ/triamterene 50/100 mg QD was co-administered with TIKOSYN (500 mcg BID) for 5 days (following 2 days of diuretic use at half dose). In patients receiving HCTZ alone, dofetilide AUC increased by 27% and C_{max} by 21%. However, the pharmacodynamic effect increased by 30% (QTc increase over time) and by 95% (maximum QTc increase). In patients receiving HCTZ in combination with triamterene, dofetilide AUC increased by 39% and C_{max} by 69%. However, the pharmacodynamic effect increased by 100% (QTc increase over time) and by 84% (maximum QTc increase). The pharmacodynamic effects can be explained by a combination of the increase in dofetilide exposure and the reductions in serum potassium. In the DIAMOND trials, 1252 patients were treated with TIKOSYN and diuretics concomitantly, of whom 493 died compared to 508 deaths among the 1248 patients receiving placebo and diuretics. Of the 229 patients who had potassium depleting diuretics added to their concomitant medications in the DIAMOND trials, the patients on TIKOSYN had a non-significantly reduced relative risk for death of 0.68 (95% CI 0.376, 1.230).

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Potential Drug Interactions

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

Dofetilide is metabolized to a small extent by the CYP3A4 isozyme of the cytochrome P450 system. Inhibitors of the CYP3A4 isozyme could increase systemic dofetilide exposure. Inhibitors of this isozyme (e.g., macrolide antibiotics,azole antifungal agents, protease inhibitors, serotonin reuptake inhibitors, amiodarone, cannabinoids, diltiazem, grapefruit juice, nefazodone, neflurxine, quinine, safinakal or ticlopidine) should be cautiously co-administered with TIKOSYN as they can potentially increase dofetilide levels. Dofetilide is not an inhibitor of CYP3A4 nor of other cytochrome P450 isozymes (e.g., CYP2C9, CYP2D6) and is not expected to increase levels of drugs metabolized by CYP3A4.

Other Drug Interaction Information

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

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

Population pharmacokinetic analyses were conducted on plasma concentration data from 1445 patients in clinical trials to examine the effects of concomitant medications on clearance or volume of distribution of dofetilide. Concomitant medications were grouped as ACE inhibitors, oral anticoagulants, calcium channel blockers, beta blockers, cardiac glycosides, inducers of CYP3A4, substrates and inhibitors of CYP3A4, substrates and inhibitors of P-glycoprotein, nitrates, sulfonylureas, 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 -10% and +7%. The mean clearances of dofetilide were 16% and 15% lower in patients on thiazide diuretics and inhibitors of tubular organic cation transport, respectively.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Dofetilide had no genotoxic effects, with or without metabolic activation, based on the bacterial mutation assay and tests of cytogenetic aberrations in vivo in mouse bone marrow and in vitro in human lymphocytes. Rats and mice treated with dofetilide in the diet for two years showed no evidence of an increased incidence of tumors compared to controls. The highest dofetilide dose
administered for 24 months was 10 mg/kg/day to rats and 20 mg/kg/day to mice. Mean doxetilide AUC(0-28d) at these doses were about 20 and 10 times, respectively, the maximum likely human AUC.

There was no effect on mating or fertility when doxetilide was administered to male and female rats at doses as high as 1.0 mg/kg/day, a dose that would be expected to provide a mean doxetilide AUC(0-28d) 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, 0.3, and 6 mg/kg/day) were associated with mean doxetilide AUCs that were about 4, 1.3, and 3 times the maximum likely human AUC, respectively.

**Pregnancy Category C**

Doxetilide has been shown to adversely affect in utero growth and survival of rats and mice when orally administered during organogenesis at doses of 2 or more mg/kg/day. Other than an increased incidence of non-osseous 5th metacarpal, and the occurrence of hydronephrosis and hydroemphraxes at doses as low as 1 mg/kg/day in the rat, structural anomalies associated with drug treatment were not observed in either species at doses below 2 mg/kg/day. The earliest drug-effect associations were for sternebral and vertebral anomalies in both species; cleft palate, adactyly, levocarida, dilution of cerebral ventricles, hydronephrosis, hydroemphraxes, 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 doxetilide AUC(0-28d) 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, doxetilide should only be administered to pregnant women where the benefit to the patient justifies the potential risk to the fetus.

**Nursing Mothers**

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

**Geriatric Use**

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

**Use in Women**

Female patients constituted 32% of the patients in the placebo-controlled trials of TIKOSYN. As with other drugs that cause Toras de Pointes, TIKOSYN was associated with a greater risk of Toras de Pointes in female patients than in male patients. During the TIKOSYN clinical development program, the risk of Toras de Pointes in females was approximately 3 times the risk in males. Unlike Toras de Pointes, the incidence of other ventricular arrhythmias was similar in female patients receiving TIKOSYN and patients receiving placebo. Although no study

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Please see full Prescribing Information, including Boxed Warning, and Medication Guide on slides 52-81, or visit www.TIKOSYNHCP.com.
Table 6: Incidence of Serious Arrhythmias and Conduction Disturbances in Patients with Supraventricular Arrhythmias

<table>
<thead>
<tr>
<th>Arrhythmia event</th>
<th>TIKOSYN dose</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;250 mg</td>
<td>1.25 mg</td>
</tr>
<tr>
<td></td>
<td>(n=227)</td>
<td>(n=212)</td>
</tr>
<tr>
<td>VT/VF (%)</td>
<td>3.5%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Ventricular Bradycardia (%)</td>
<td>1.7%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Torsade de Pointes (%)</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

* Patients with more than one arrhythmia are counted only once in this category.

In the DIAMOND trials, a total of 1,511 patients were exposed to TIKOSYN for 1.757 patient years. The incidence of Torsade de Pointes was 3.3% in CHF patients and 0.9% in patients with a recent MI.

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

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

<table>
<thead>
<tr>
<th>Arrhythmia event</th>
<th>TIKOSYN</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=224)</td>
<td>(n=227)</td>
</tr>
<tr>
<td>VT/VF (%)</td>
<td>1.8%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Ventricular Bradycardia (%)</td>
<td>2.7%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Torsade de Pointes (%)</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

* Patients with more than one arrhythmia are counted only once in this category.

Other Adverse Reactions: Table 8 presents other adverse events reported with a frequency of >2% on TIKOSYN and reported numerically more frequently on TIKOSYN than on placebo in the studies of patients with supraventricular arrhythmias.
Table 8: Frequency of Adverse Events Occurring at ≥2% on TIKOSYN, and Numerically More Frequently on TIKOSYN than Placebo in Patients with Supraventricular Arrhythmias

<table>
<thead>
<tr>
<th>Adverse Event</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>vitreous</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>

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

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

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

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

**OVERDOSAGE**

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

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

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

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

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

**DOSAGE AND ADMINISTRATION**

- Therapy with TIKOSYN must be initiated (and, if necessary, re-initiated) in a setting that provides continuous electrocardiographic (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 three days. Additionally, patients should not be discharged within 12 hours of electrical or pharmacological conversion to normal sinus rhythm.

- The dose of TIKOSYN must be individualized according to calculated creatinine clearance 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 dose of TIKOSYN is 500 mcg BID, as modified by the dosing algorithm described below. For consideration of a lower dose, see Special Considerations below.

- 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 3.6-4.0 mEq/L.
• Patients with atrial fibrillation should be anticoagulated according to usual medical practice prior to electrical or pharmacological 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.

• 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 upon 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 received one of the education programs.

**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 5–10 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 <50 beats per minute have not been studied.

**Step 2.** Calculation of creatinine clearance: Prior to the administration of the first dose, the patient’s creatinine clearance must be calculated using the following formula:

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

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

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

**Step 3.** Starting Dose: The starting dose of TIKOSYN is determined as follows:

- **Calculated Creatinine Clearance**
  - \(<60 \text{ mL/min}\)
  - \(40 - 60 \text{ mL/min}\)
  - \(20 - 40 \text{ mL/min}\)
  - \(\leq 20 \text{ mL/min}\)

- **TIKOSYN Dose**
  - 500 mg twice daily
  - 250 mg twice daily
  - 125 mg twice daily
  - Dofetilide is contraindicated in these patients

**Step 4.** administer the adjusted TIKOSYN dose and begin continuous ECG monitoring.
Step 5. At 2–3 hours after administering the first dose of TIKOSYN, determine the QTc. If the QTc has increased by greater than 15% compared to the 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:

- **If the Starting Dose Based on**
  - Creatinine Clearance is:
  - 500 mcg twice daily
  - 250 mcg twice daily
  - 125 mcg twice daily

- **Then the Adjusted Dose**
  - (for QTc Prolongation is):
  - 250 mcg twice daily
  - 125 mcg twice daily
  - 125 mcg once a day

Step 6. At 2–3 hours after each subsequent dose of TIKOSYN, determine the QTc (for in-hospital doses 2–5). No further down titration 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 three days, or for a minimum of 12 hours after electrical or pharmacological conversion to normal sinus rhythm, whichever is greater.

The steps described above are summarized in the following diagram.
Please see full Prescribing Information, including Boxed Warning, and Medication Guide on slides 52-81, or visit www.TIKOSYNHCP.com.
Maintenance of TIKOSYN Therapy
Renal function and QTc should be re-evaluated every three months or as medically warranted. If QTc exceeds 500 milliseconds (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 above should be used to determine the individualized dose of TIKOSYN. In clinical trials (see CLINICAL STUDIES), the highest dose of 500 mcg BID of TIKOSYN as modified by the dosing algorithm led to greater effectiveness than lower doses of 125 or 250 mcg BID as modified by the dosing algorithm. The risk of Toradie de Pointes, 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 the lower dose is increased, the patient needs to be rehospitalized for three days. Previous toleration of higher doses does not eliminate the need for readmission.

The maximum recommended dose in patients with a calculated creatinine clearance greater than 60 mL/min is 500 mcg BID; doses greater than 500 mcg BID have been associated with an increased incidence of Toradie de Pointes.

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 normal sinus rhythm 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 post cardioversion, or a minimum of 3 days after initiation of TIKOSYN therapy, whichever is greater.

Switch 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 three (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 three months.

Stopping TIKOSYN Prior to Administration of Potentially Interacting Drugs
If TIKOSYN needs to be discontinued to allow dosing of other potentially interacting drug(s), a washout period of at least two days should be followed before starting the other drug(s).

HOW SUPPLIED
TIKOSYN® 125 mcg (0.125 mg) capsules are supplied as No. 4 capsules with a light orange cap and white body, printed with TKN 125 PFIZER, and are available in:
TIKOSYN® 250 mcg (0.25 mg) capsules are supplied as No. 4 capsules, peach cap and body, printed with TKN 250 PFIZER, and are available in:

TIKOSYN® 500 mcg (0.5 mg) capsules are supplied as No. 2 capsules, peach cap and white body, printed with TKN 500 PFIZER, and are available in:

<table>
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<tr>
<th></th>
<th>125 mcg (0.125 mg)</th>
<th>250 mcg (0.25 mg)</th>
<th>500 mcg (0.5 mg)</th>
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<tr>
<td>Obverse</td>
<td>TKN 125</td>
<td>TKN 250</td>
<td>TKN 500</td>
</tr>
<tr>
<td>Reverse</td>
<td>PFIZER</td>
<td>PFIZER</td>
<td>PFIZER</td>
</tr>
<tr>
<td>Bottle of 14</td>
<td>0069-5800-61</td>
<td>0069-5810-61</td>
<td>0069-5820-61</td>
</tr>
<tr>
<td>Bottle of 60</td>
<td>0069-5800-60</td>
<td>0069-5810-60</td>
<td>0069-5820-60</td>
</tr>
<tr>
<td>Unit dose / 40</td>
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<td>0069-5810-43</td>
<td>0069-5820-43</td>
</tr>
</tbody>
</table>

Store at controlled room temperature, 15° to 30°C (59° to 86°F). PROTECT FROM MOISTURE AND HUMIDITY. Dispense in tight containers (USP). Rx only

LAB-0067-6.0
Revised February 2011

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MEDICATION GUIDE
TIKOSYN® (tee' ko sin)
dofetilide Capsules

Read the Medication Guide before you start taking TIKOSYN and each time you get a refill.
This information does not take the place of talking with your doctor about your condition or
treatment.

What is the most important information I should know about TIKOSYN?
TIKOSYN can cause serious side effects, including a type of abnormal heartbeat called
Torsade de Pointes, which can lead to death.
To establish the right dose of TIKOSYN, treatment with TIKOSYN must be started in a hospital
where your heart rate and kidney function will be checked for the first 3 days of treatment. It is
important that when you go home, you take the exact dose of TIKOSYN that your doctor
prescribed for you.
While you take TIKOSYN, always watch for signs of abnormal heartbeat.
Call your doctor and go to the hospital right away if you:
• feel faint
• become dizzy, or
• have a fast heartbeat

What is TIKOSYN?
TIKOSYN is a prescription medicine that is used to treat an irregular heartbeat (atrial fibrillation or atrial
flutter).
It is not known if TIKOSYN is safe and effective in children under 18 years of age.

Who should not take TIKOSYN?
Do not take TIKOSYN if you:
• have an irregular heartbeat called long QT syndrome
• have kidney problems or are on kidney dialysis
• take any of these medicines:
  • cimetidine (TAGAMET, TAGAMET HB®)
  • verapamil (CALAN, CALAN SR, COVERA-HS, ISOPTIN, ISOPTIN SR,
    VERelan, VERelan PM, TARXIA®)
  • ketoconazole (NIZoral, XOLEGEL, EXTRAZOL)*
  • trimethoprim alone (PROLOPRIM, TRIMPEX®) or the combination of
    trimethoprim and sulfamethoxazole (BACTRIM, SEPTRA SULFATRIM®)*
  • prochlorperazine (COMPAZINE, COMPO®)
  • mexitelol (MEGACE®)
  • hydrochlorothiazide alone or in combination with other medicines (such as ESIDrix,
    EZIDE, HYDRODIURIL, HYDRO-FAR, MICROZIDE, or ORETIC®)*
  • Ask your doctor if you are not sure if any of your medicines are the kind listed above.
  • are allergic to dofetilide in TIKOSYN. See the end of this leaflet for a complete

Please see full Prescribing Information, including Boxed Warning, and Medication
Guide on slides 52-81, or visit www.TIKOSYNHCP.com.
list of ingredients in TIKOSYN.

What should I tell my doctor before taking TIKOSYN?
Before taking TIKOSYN, tell your doctor about all of your medical conditions including if you:

- have heart problems
- have kidney or liver problems
- are pregnant or plan to become pregnant. It is not known if TIKOSYN will harm your unborn baby.
- are breast-feeding or plan to breast-feed. It is not known if TIKOSYN passes into your breast milk. You and your doctor should decide if you will take TIKOSYN or breast-feed. You should not do both.

Especially tell your doctor if you take medicines to treat:

- heart problems
- high blood pressure
- depression or other mental problems
- asthma
- allergies, or hay fever
- skin problems
- infections

Ask your doctor if you are not sure about the medicines you take. Tell your doctor about all prescription and non-prescription medicines, vitamins, dietary supplements, and any natural or herbal remedies. TIKOSYN and other medicines may affect each other, causing serious side effects. If you take TIKOSYN with certain medicines, you will be more likely to have a different type of abnormal heartbeat. See “Who should not take TIKOSYN?”

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

How should I take TIKOSYN?

- Take TIKOSYN exactly as your doctor tells you.
- Do not change your TIKOSYN dose unless your doctor tells you to.
- Your doctor will do tests before you start and while you take TIKOSYN.
- Do not stop taking TIKOSYN until your doctor tells you to stop. If you miss a dose, just take the next dose at your regular time. Do not take 2 doses of TIKOSYN at the same time.
- TIKOSYN can be taken with or without food.
- If you take too much TIKOSYN, call your doctor or go to the nearest hospital emergency room right away. Take your TIKOSYN capsules with you to show to the doctor.

What are the possible side effects of TIKOSYN?

TIKOSYN can cause serious side effects, including a type of abnormal heartbeat called "Torsade de Pointes, which can lead to death. See "What is the most important information I should know about TIKOSYN?"

The most common side effects of TIKOSYN include:
• headache
• chest pain
• dizziness

Call your doctor right away if you have signs of electrolyte imbalance:
• severe diarrhea
• unusual sweating
• vomiting
• not hungry (loss of appetite)
• increased thirst (drinking more than normal)

Tell your doctor if you have any side effects that bother you or do not go away.

These are not all the possible side effects of TIKOSYN. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TIKOSYN?
• Store TIKOSYN between 59° to 86°F (15° to 30°C).
• Keep TIKOSYN away from moisture and humidity.
• Keep TIKOSYN in a tightly closed container.
• Keep TIKOSYN and all medicines out of the reach of children.

General information about TIKOSYN
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TIKOSYN for a condition for which it was not prescribed. Do not give TIKOSYN to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about TIKOSYN. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about TIKOSYN that is written for health professionals.

For more about TIKOSYN, go to www.tikosyn.com or call 1-877-TIKOSYN (1-877-845-8796).

What are the ingredients in TIKOSYN?
Active ingredient: dofetilide
Inactive ingredients:
- Capsule fill: microcrystalline cellulose, corn starch, colloidal silicon dioxide, and magnesium stearate
- Capsule shell: gelatin, titanium dioxide, and FD&C Yellow 6
- Imprinting ink: iron oxide black, shellac, n-butyl alcohol, isopropyl alcohol, propylene glycol, and ammonium hydroxide

* Listed trademarks are the property of their respective owners.

Rx only

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