To request additional TIKOSYNtogether Support Kits for your patients, please visit www.TIKOSYNHCP.com/TIKOSYNtogether or call 1-877-TIKOSYN.
TIKOSYN® (dofetilide): demonstrated efficacy and safety profile

**Efficacy**

In 2 randomized, parallel, double-blind, placebo-controlled, dose-response studies, TIKOSYN converted patients with atrial fibrillation/atrial flutter (AF/AFL) of more than 1 week duration to normal sinus rhythm (NSR) and maintained NSR after drug-induced or electrical cardioversion.

**Safety profile**

In the 2 DIAMOND studies, TIKOSYN did not increase mortality in AF/AFL patients with structural heart disease (SHD) and relatively high risk of sudden death vs placebo. Additionally, TIKOSYN was associated with reduced risk of hospitalization due to the worsening of congestive heart failure (CHF) in New York Heart Association (NYHA) Class II/IV CHF patients (risk ratio: 0.75; 95% CI: 0.63-0.89) in one of the 2 studies.

**TIKOSYN® (dofetilide) has been in clinical use for more than 10 years**

TIKOSYN has been used effectively in patients with NYHA Class I-IV CHF.

**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 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.

Helping support you and your highly symptomatic AF/AFL patients with TIKOSYN® (dofetilide)

The TIKOSYNtogether™ Support Program is a simple, easy way to supplement the care you and your team provide to your highly symptomatic AF/AFL patients. The program can help you support your TIKOSYN patients by offering them:

**SAVINGS**

- TIKOSYN $10 Co-pay Card—eligible patients get TIKOSYN for as little as $10 per month*

*For eligible patients. Terms and Conditions apply. Please see page 7. This card is only valid at participating pharmacies. No membership fees. www.TIKOSYNHCP.com, Pfizer Inc, 235 E. 42nd Street, New York, NY 10017, 1-877-TIKOSYN.

**REFILLS**

- Help finding the certified pharmacy nearest them
- Prescription delivery option—directly to your patients’ homes or offices

**SUPPORT**

- Educational guides clearly explaining AF/AFL, how TIKOSYN works, proper dosing, and what treatment initiation involves
- An extended-hours Nurse Hotline patients can call for help and support
- Additional materials, including lifestyle and treatment tips

Enclosed, you’ll find your TIKOSYNtogether Support Kits. These were designed to help you introduce your patients to TIKOSYN and to provide them with valuable information and support.

This brochure will walk you through everything included in the Support Kit and how its components can help you support your patients.
Suggested Use:

Make sure your patients know about this Co-pay Card so they can easily pay for their TIKOSYN prescriptions. Remind them that they should bring the card with them to the pharmacy every time they fill their prescription. During a conversation about this card, you may also want to discuss the need to fill a TIKOSYN prescription at a REMS-certified pharmacy.

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.

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.

Please see enclosed full Prescribing Information, including Boxed Warning, and Medication Guide beginning on page 8.
Please see additional Important Safety Information on page 6.
A guide to TIKOSYN® (dofetilide)

Brochure

After your patients have learned about AF/AFL, they may want to know more about TIKOSYN. This brochure should help you explain the medication to them. Based on the Medication Guide, it is written in clear, patient-friendly language, making it a great way for patients to learn about TIKOSYN. The topics covered in the About TIKOSYN brochure include:

- What is TIKOSYN?
- Why is TIKOSYN therapy initiated in the hospital?
- Who should not take TIKOSYN? (contraindications and interactions)
- How to take TIKOSYN
- TIKOSYN side effects

Suggested Use:

Starting a dialogue with your patients about TIKOSYN, how it is initiated, and how it can affect them is very important. This brochure can help facilitate that discussion. Used in conjunction with the Medication Guide, this pamphlet can answer many of the questions that patients often ask you about TIKOSYN. For instance, if patients have questions about how to use TIKOSYN, or how it’s initiated, this brochure can be used to respond.

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.

Selected Safety Information

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

Please see enclosed full Prescribing Information, including Boxed Warning, and Medication Guide beginning on page 8.

Please see additional Important Safety Information on page 6.

Hospital Tip Sheet

In order to mitigate the risk of induced arrhythmia, the TIKOSYN® (dofetilide) REMS requires new patients be initiated in a hospital setting. Your patients may have questions about why this is needed and what to expect during their hospital stay. This brochure can help answer those questions and help patients learn:

- Why TIKOSYN is initiated in the hospital
- What they can expect during their hospital stay
- How they may want to prepare for their stay
- What they can do to pass the time during their stay
- About their discharge and subsequent access to TIKOSYN

Suggested Use:

If patients ask you about their 3-day hospital start, the first page of this brochure can be used to help answer their questions. Your patients may have some misconceptions about what their hospital stay will entail when starting TIKOSYN. Use this brochure to help answer questions they may have about the TIKOSYN initiation by letting them know they’ll be:

- In the hospital to find the right dose of TIKOSYN
- Monitored continuously to avoid induced arrhythmia
- Undergoing minimal, non-invasive testing

You can also use this tip sheet to give your patients clear steps on how to secure TIKOSYN outside of the hospital so you can be sure they’re prepared for their discharge.
Medicine Tracker Card

Your TIKOSYN® (dofetilide) patients may be on numerous medications, and this card can make it easier for you, your colleagues, and your patients to keep track.

In addition to providing a chart in which you and your patients can list their medications, this card includes a list of drug interactions to help them remember what drugs they should not take while on TIKOSYN. It also contains quick, clear guidance to patients on what to do if they miss a dose or take too much.

All of these elements work together to help your patients take their medications correctly.

Suggested Use:

Filling out this card with your patients can be an opportunity to have a larger conversation about the best times to take TIKOSYN and why they must follow all directions when taking their medications.

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.

TIKOSYNtogether™ Support Program Brochure

By introducing patients to the TIKOSYNtogether Support Program, this brochure shows them the resources that are available only with a prescription for TIKOSYN® (dofetilide). In addition to describing what is included in the TIKOSYNtogether Support Kit, it also provides information on the offerings that go beyond the kit.

Additional resources of the TIKOSYNtogether Support Program:

- **Pharmacy Support**—TIKOSYN is only available at REMS-certified pharmacies. Our Find A Pharmacy feature can help your patients locate the pharmacy nearest them. Patients can also sign up to have TIKOSYN prescriptions delivered directly to their homes or offices. They can learn more:
  - Online—at www.TIKOSYN.com
  - Phone—by calling 1-877-TIKOSYN
- **Nurse Hotline**—This extended-hours Nurse Hotline takes your support of your patients a step further by giving them access to a nurse who can quickly answer the most frequently asked questions about TIKOSYN
- **TIKOSYNtogether Newsletter**—Patients enrolled in TIKOSYNtogether receive a periodic newsletter offering lifestyle tips, advice, and program updates

Suggested Use:

Your patients may be eager to hear about the additional support they’ll be receiving when they sign up for the TIKOSYNtogether Support Program. This brochure can help you guide them through what is available. You may want to indicate specific components of the program that may help individual patients.
Indication

TIKOSYN® (dofetilide) 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.

Important Safety Information

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

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.

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 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.

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

Please see enclosed full Prescribing Information, including Boxed Warning, and Medication Guide beginning on page 8.

Terms & Conditions

By using the TIKOSYN® (dofetilide) $10 Co-pay Card (the “Card”), you acknowledge that you currently meet the eligibility criteria and will comply with the Terms and Conditions described below:

• This Card is not valid for prescriptions that are eligible to be reimbursed, in whole or in part, by Medicaid, Medicare or other federal or state healthcare programs (including any state prescription drug assistance programs and the Government Health Insurance Plan available in Puerto Rico [formerly known as “La Reforma de Salud”])
• The Card is not valid for prescriptions that are eligible to be reimbursed by private insurance plans or other health or pharmacy benefit programs which reimburse you for the entire cost of your prescription drugs
• To qualify for this offer, your out-of-pocket expense must be greater than $10 per prescription. If your out-of-pocket expenses for a 1-month supply (60 capsules) are $110 or less, you will pay $10 for a 1-month supply. If your out-of-pocket expenses for a 1-month supply (60 capsules) exceed $110, you qualify for up to $100 in savings for a 1-month supply. In either case, you can only qualify for up to $1,200 of savings per calendar year. After maximum of $1,200, you will pay usual monthly out-of-pocket costs
• You must deduct the value received under this program from any reimbursement request submitted to your insurance plan, either directly by you or on your behalf
• The Card is not valid where otherwise prohibited by law
• This Card cannot be combined with any other rebate/coupon, free trial or similar offer for the specified prescription
• The Card will be accepted only at participating pharmacies
• This Card is not health insurance
• Offer good only in the U.S. and Puerto Rico
• The Card is limited to 1 per person during this offering period and is not transferable
• Offer limited to 1 use per month
• Pfizer reserves the right to rescind, revoke or amend the program without notice at any time
• Card and Program expire 7/1/2015
• No membership fees

For reimbursement when using a nonparticipating pharmacy/mail order: Pay for your TIKOSYN prescription and mail a copy of original pharmacy receipt (cash register receipt NOT valid) with product name, date, and amount circled to:

TIKOSYN Rebates
PO Box 2242
Morrisville, PA 19067-0542

Be sure to include a copy of the front of your Co-pay Card and your name and mailing address.

For more information, please call 1-877-TIKOSYN or visit www.TIKOSYNHCP.com.
Pfizer Inc, 235 E. 42nd Street, New York, NY 10017.
The chemical name for dofetilide is:

\[
\text{C}_{19}\text{H}_{27}\text{N}_{3}\text{O}_{5}\text{S}_{2}
\]

and it has a molecular weight of 441.6. The structural formula is as follows:

\[
\text{HO}_2\text{C}_19\text{H}_{27}\text{N}_{3}\text{O}_{5}\text{S}_{2}\text{NH}_2\text{CO}_2\text{H}
\]

Absorption and Distribution: The oral bioavailability of dofetilide is >90%, with maximal plasma concentrations occurring in patients with pre-existing heart block and/or sick sinus syndrome.

In patients, dofetilide is extensively metabolized primarily in the liver, with formation of metabolites that are predominantly conjugates of glucuronic acid and small amounts of free acid. The total area under the curve of the metabolites is about 10% of the parent compound, with approximately 20% of the urinary dose recovered as unchanged drug. Dofetilide is highly protein bound (>99%) in plasma.

Mechanism of Action

TIKOSYN (dofetilide) is a potassium channel blocker. The molecular formula of dofetilide is C19H27N3O5S2. It is a white to off-white powder. It is slightly soluble in water and practically insoluble in 0.1 M aqueous sodium hydroxide or hydrochloric acid.

TIKOSYN capsules contain the following inactive ingredients: microcrystalline cellulose, starch, colloidal silicon dioxide, magnesium stearate, and a film coat containing polyethylene glycol, titanium dioxide, and red iron oxide. TIKOSYN is supplied for oral administration in three dosage strengths: 125 mcg, 250 mcg, and 500 mcg.

CLINICAL PHARMACOLOGY

TIKOSYN capsules contain the following inactive ingredients: microcrystalline cellulose, starch, colloidal silicon dioxide and magnesium stearate. TIKOSYN is supplied for oral administration in three dosage strengths: 125 mcg, 250 mcg, and 500 mcg.

CLINICAL STUDIES

Chronic Atrial Fibrillation and/or Atrial Flutter

Two randomized, parallel, double-blind, placebo-controlled, dose-response trials evaluated the ability of TIKOSYN to convert patients with atrial fibrillation or atrial flutter (AF/AA) of more than 1 week duration to normal sinus rhythm (NSR) and to maintain NSR (delay time to recurrence of AF/AA) after drug-induced or electrical cardioversion. A total of 986 patients with a one to two history of atrial fibrillation/atrial flutter were enrolled. Both studies randomized patients to placebo or to doses of TIKOSYN 125 mg, 250 mg, 500 mcg, or in one study a comparator drug, given twice a day. The 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 syncpe within the past 6 months, AV block greater than first degree, MR 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 >460 ms, QRS prolongation >0.25 second, or are sensitized to dofetilide.

In both studies, enrolled mostly Caucasians (over 90%), males (over 70%), and patients with AF/AA of one year or more (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 concurrent therapy, including digoxin (over 60%), diuretics (over 20%), and antiarrhythmics (over 30%). 10% of patients were on antiplatelet agents.

Acute conversion rates are shown in Table 1 for randomized doses (doses were adjusted for calculated creatinine clearance and, in one of the studies, 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>Dose (mg)</th>
<th>Baseline QTc (ms)</th>
<th>TIKOSYN QTc (ms)</th>
<th>Placebo QTc (ms)</th>
<th>Baseline NSR (%)</th>
<th>TIKOSYN NSR (%)</th>
<th>Placebo NSR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>5/82(6%)</td>
<td>8/82(10%)</td>
<td>77/84(93%)</td>
<td>38%</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>Study 2</td>
<td>6/135(4%)</td>
<td>14/133(11%)</td>
<td>58/129(47%)</td>
<td>1/84(1%)</td>
<td>1/84(1%)</td>
<td>1/84(1%)</td>
</tr>
</tbody>
</table>

Patients who did not convert with TIKOSYN randomization 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. TIKOSYN is highly protein bound (>99%) and is extensively metabolized in the liver, with formation of metabolites that are predominantly conjugates of glucuronic acid and small amounts of free acid. The total area under the curve of the metabolites is about 10% of the parent compound, with approximately 20% of the urinary dose recovered as unchanged drug. Dofetilide is highly protein bound (>99%) in plasma.
studied 1518 patients hospitalized with severe CHF who had confirmed impaired left ventricular function (ejection fraction ≤ 35%). Patients were randomized to treatment with TIKOSYN (n=760), placebo (n=756). The probability of survival at one year was 73% (95% CI: 76% – 80%) in the TIKOSYN group and 72% (95% CI: 69% – 74%) in the placebo group. Similar efficacy results were seen for cardiac deaths and arrhythmic deaths, as shown in Table 2 (p-values vs. placebo for cardiac death: P=0.21, P=0.10, P<0.001, and for arrhythmic death: P=0.006, P=0.001, P<0.001). Median time to recurrence (days) was 182 for TIKOSYN and >365 for placebo (p<0.001). The point estimates of the probabilities of remaining in NSR at 6 and 12 months were 62% and 58%, respectively, for TIKOSYN 500 mcg BID and 35%. 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=757). The probability of survival at one year was 72% (95% CI: 75% – 76%) in the TIKOSYN group and 71% (95% CI: 68% – 74%) in the placebo group. The concomitant use of hydrochlorothiazide (alone or in combination with triamterene) with TIKOSYN is contraindicated (see Drug-Drug Interactions). Dofetilide should be used for a minimum of three days in a facility where qualified personnel are available to monitor patients for serious ventricular arrhythmias. Calculation of the creatinine clearance for all patients must precede administration of dofetilide. 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 dofetilide. For detailed instructions regarding dose selection, see DOSAGE and ADMINISTRATION. The risk of dofetilide induced ventricular arrhythmias 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; and 3) by observing the overall mortality rate in patients with atrial fibrillation and in patients with structural heart disease. The concomitant use of verapamil or the calcium transport inhibitor inhibitors cilostamide, trimetazidine (alone or in combination with sulfamethoxazole), or ketoconazole with TIKOSYN is contraindicated (see WARNINGS and Drug-Drug Interactions). as each of these drugs cause a substantial increase in dofetilide plasma concentrations. In addition, other known inhibitors of the renal calcium transport system such as propafenone and mexitelene should not be used in patients on TIKOSYN. The concomitant use of hydrochlorothiazide (alone or in combination with sulfinpyrazone or TIKOSYN is contraindicated (see PREGNANCY, 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. Ventricular Arrhythmia: TIKOSYN (dofetilide) can cause serious ventricular arrhythmias, primarily Torso de Points (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 recent creatinine clearance or certain dofetilide drug interactions will increase dofetilide plasma concentration. The risk of TDP can be reduced by controlling the plasma concentration and arrhythmia adjustment of the QT interval based on clinical dose 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 QT interval and its relation to the dose and plasma concentration of dofetilide. For detailed instructions regarding dose selection, see DOSAGE and ADMINISTRATION. 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Capsules

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

Table 4: Summary of Torsade de Pointes in Patients Randomized to Dofetilide by Dose

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Torsade de Pointes</th>
</tr>
</thead>
<tbody>
<tr>
<td>891</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>891</td>
<td>3 (0.3%)</td>
</tr>
<tr>
<td>891</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>891</td>
<td>11 (1.2%)</td>
</tr>
</tbody>
</table>

As shown in Table 4, the rate of TDP was reduced when patients were dosed according to their renal function (see CLINICAL PHARMACOKINETICS, Pharmacokinetics in Special Populations, Renal Impairment and ADMINISTRATION). The majority of the episodes of TDP occurred within the first three days of TIKOSYN therapy (101 events in the 101 patients with supraventricular arrhythmias: 1 event in 171 dofetilide and 117 placebo, and 4 events in the placebo group). Adjusted for duration of therapy, primary diagnosis, age, gender, and prevalence of structural heart disease, the point estimate of the hazard ratio for the pooled studies (TIKOSYN/placebo) was 1.19 (95% CI: 1.3, 3.3). The DIAMOND CHF and MI trials examined mortality in patients with structural heart disease, rejection fraction <35%. In these two large, double-blind studies, deaths occurred in 36% (54/151) of TIKOSYN-treated patients and 39% (57/147) of placebo patients. In an analysis of 560 DIAMOND patients with atrial fibrillation/flutter at baseline, one year mortality was 15% in the TIKOSYN-treated group and 12% in the placebo group. Of the 560 patients, there were no 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 isozyme 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 inhibitors of this process have been shown to increase systemic exposure of dofetilide. Therefore, the effect on renal elimination by citalopram, thioridapine, and tizanidine should be cautiously interpreted. Although the effect on CYP3A4 and renal elimination of theophylline and azithromycin is not known, these agents should be used with caution in patients receiving TIKOSYN. In multiple studies, there were no deaths in TIKOSYN-treated patients given placebo (see CLINICAL STUDIES).

Hypokalemia and Potassium-Depleting Diuretics Use of TIKOSYN in conjunction with other drugs that prolong the QT interval has not been studied and is not recommended. Certain diuretics (thiazides, spirolactones, loop diuretics, aminoguanidine, amiloride) are potent inhibitors of renal potassium transport. Inhibitors of renal potassium transport (e.g., cimetidine, ranitidine, 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 co-administered with TIKOSYN (500 mcg BID) for 7 days. In these patients, potassium (alone or in combinations such as with triamterene) (see WARNINGS, CONTRAINDICATIONS) should be monitored and potassium replacement therapy should be used as alternatives to cimetidine, as these agents have no effect on the pharmacokinetic profile of TIKOSYN.

Potassium deficiency is one of the most consistent findings in chronic dofetilide treatment, with over 90% of patients receiving dofetilide having a baseline serum potassium level of less than 4.5 mmol/L. Administration of potassium is recommended. The risk of torsades de pointes is increased with potassium levels of less than 3.0 mmol/L and the electrocardiogram should be monitored closely in these patients. Reversal of Torsade de Pointes with a potassium-sparing diuretic (spironolactone, amiloride, triamterene) should be considered.

Use with Drugs that Prolong QT Interval and Antiarrhythmic Agents Patients with structural heart disease in patients on digoxin; structural heart disease is a known risk factor for arrhythmia. No increase in the point estimate of the hazard ratio for the pooled studies (TIKOSYN/placebo) was 1.19 (95% CI: 1.3, 3.3). The DIAMOND CHF and MI trials examined mortality in patients with structural heart disease, rejection fraction <35%. In these two large, double-blind studies, deaths occurred in 36% (54/151) of TIKOSYN-treated patients and 39% (57/147) of placebo patients. In an analysis of 560 DIAMOND patients with atrial fibrillation/flutter at baseline, one year mortality was 15% in the TIKOSYN-treated group and 12% in the placebo group. Of the 560 patients, there were no more deaths in TIKOSYN-treated patients than in patients given placebo (see CLINICAL STUDIES).

TIKOSYN® Capsules

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

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

Drug/Laboratory Test Interactions

None known.

Drug-Drug Interactions

Cimetidine: (see WARNINGS, CONTRAINDICATIONS) Co-administration of cimetidine with TIKOSYN has 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 coadministration of cimetidine with dofetilide was associated with a higher incidence of Torsade de Pointes.

Ketoconazole: (see WARNINGS, CONTRAINDICATIONS) Co-administration of ketoconazole is contraindicated. Ketoconazole at 400 mg daily (the maximum approved dose of ketoconazole) co-administered with TIKOSYN (500 mcg BID) for 7 days has been shown to increase dofetilide AUC by 54.9% in males and 79% in females, and AUC by 45% in males and 66% in females.

Trimethoprim Alone or in Combination with Sulfamethoxazole: (see WARNINGS, CONTRAINDICATIONS) Use of sulfonamide antibacterials in patients with significant heart disease (DIAMOND CHF, MI) has not been studied. Torsade de Pointes has been reported in patients with Torsade de Pointes. It is not clear whether this represents an interaction with TIKOSYN or the presence of more severe structural heart disease in these patients.

Hypokalemia and Potassium-Depleting Diuretics Use of TIKOSYN in conjunction with other drugs that prolong the QT interval has not been studied and is not recommended. Certain diuretics (thiazides, spirolactones, loop diuretics, aminoguanidine, amiloride) are potent inhibitors of renal potassium transport. Inhibitors of renal potassium transport (e.g., cimetidine, ranitidine, 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 co-administered with TIKOSYN (500 mcg BID) for 5 days. In these 2 days of diuretic use at half dose. In patients receiving TIKOSYN was 31% vs. 32% on placebo (see WARNINGS, CONTRAINDICATIONS).

Use with Drugs that Prolong QT Interval and Antiarrhythmic Agents Patients with structural heart disease in patients on digoxin; structural heart disease is a known risk factor for arrhythmia. No increase in the point estimate of the hazard ratio for the pooled studies (TIKOSYN/placebo) was 1.19 (95% CI: 1.3, 3.3). The DIAMOND CHF and MI trials examined mortality in patients with structural heart disease, rejection fraction <35%. In these two large, double-blind studies, deaths occurred in 36% (54/151) of TIKOSYN-treated patients and 39% (57/147) of placebo patients. In an analysis of 560 DIAMOND patients with atrial fibrillation/flutter at baseline, one year mortality was 15% in the TIKOSYN-treated group and 12% in the placebo group. Of the 560 patients, there were no more deaths in TIKOSYN-treated patients than in patients given placebo (see CLINICAL STUDIES).

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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 Torsade de Pointes, TIKOSYN was associated with a greater risk of Torsade de Pointes in female patients than in male patients. During the TIKOSYN clinical development program, the risk of Torsade de Pointes in females was approximately 3 times the risk in males. Unlike Torasemide, the incidence of other ventricular arrhythmias was similar in female patients receiving TIKOSYN and patients receiving placebo. Although no specific study has investigated this point, in post-hoc analyses, no increased mortality was observed in females on TIKOSYN compared to females on placebo.

Pediatric Use

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

ADVERSE REACTIONS

The TIKOSYN clinical program involved approximately 9,400 patients in 130 clinical studies of normal volunteers and patients with supraventricular and ventricular arrhythmias. TIKOSYN was administered to 5,184 patients, including two large, placebo-controlled mortality trials (DIAMOND CHF and DIAMOND MI) in which 1,511 patients received TIKOSYN for up to three years.

In the following section, adverse reaction data for cardiac arrhythmias and non-cardiac adverse reactions are presented separately for patients included in the supraventricular arrhythmia development program and for patients included in the DIAMOND CHF and MI mortality trials (see CLINICAL STUDIES, Safety in Patients with Structural Heart Disease, DIAMOND Studies, for a description of these trials).

In studies of patients with supraventricular arrhythmias, a total of 1,346 and 677 patients were exposed to TIKOSYN and placebo for 551 and 207 patient years, respectively. A total of 8.7% of patients in the dofetilide groups were discontinued from clinical trials due to adverse events compared to 8.0% in the placebo groups. The most frequent reason for discontinuation (1%) was ventricular tachycardia (2.0% on dofetilide vs. 1.3% on placebo). The most frequent adverse events were headache, chest pain, and dizziness.

Serious Arrhythmias and Conduction Disturbances: Torsade de Pointes is the only arrhythmia that showed a dose-dependent relationship to TIKOSYN treatment. It does not occur in placebo treated patients. The incidence of Torsade de Pointes in patients with supraventricular arrhythmias was 0.8% (11/1346) (see WARNINGS). The incidence of Torsade de Pointes in patients who were dosed according to the recommended dosing regimen (see DOSAGE AND ADMINISTRATION) was 0.8% (4/485). Table 6 shows the frequency by randomized dose of serious arrhythmias and conduction disturbances reported as adverse events in patients with supraventricular arrhythmias.

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

<table>
<thead>
<tr>
<th>TIKOSYN Dose</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=217</td>
<td>N=388</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>3.7%</td>
</tr>
<tr>
<td>Incidence</td>
<td>3.4%</td>
</tr>
<tr>
<td>Torsade de Points</td>
<td>0.3%</td>
</tr>
<tr>
<td>Total</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

Ventricular tachycardia was 0.3% on TIKOSYN and 0.1% on placebo.

In the DIAMOND trials, a total of 1,511 patients were exposed to TIKOSYN for 1757 patient years. The incidence of Torsade de Pointes in patients was 3.3% in CHF patients and 0.5% in patients with a recent MI. In the DIAMOND MI trial, the incidence of Torsade de Pointes was 3.1% (6/193) on TIKOSYN and 0.4% (1/261) on placebo.

The following adverse events have been reported with a frequency of <1% and numerically more frequently with TIKOSYN than placebo in patients with supraventricular arrhythmias: angioedema, bradycardia, cerebral ischaemia, cerebrovascular accident, epilepsy, facial palsy, fasciculation, fever, flu syndrome, heart arrest, increased cough, liver damage, malignancy, myocardial infarction, paralyisis, pantonemia, sudden death, syncope.

The incidences of clinically significant laboratory test abnormalities in patients with supraventricular arrhythmias were similar on TIKOSYN and those on placebo. No clinically relevant effects were observed.

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 overdosage is likely to be excessive prolongation of the QT interval.

In cases of overdose, cardiac monitoring should be initiated. Charcoal slurry may be given soon after overdosing but has been useful only when given within 15 minutes of TIKOSYN administration. Treatment of Torsade de Pointes or overdose may include administration of intravenous magnesium, 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 dobutamine-induced prolongation of atrial and ventricular effective refractory periods in a dose-dependent manner. Magnesium sulfate, administered parenterally either intravenously or orally in a dog model, was effective in the prevention of dobutamine-induced Torasemide-induced tachycardia. Similarly, in man, intravenous magnesium sulfate may terminate Torsade de Pointes, irrespective of cause.

TIKOSYN overdoses were rare in clinical trials; there were two reported cases of TIKOSYN overdoses in the oral clinical program. One patient resolved 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 2000 mg doses one hour apart and experienced ventricular fibrillation and cardiac arrest 3 hours after the second dose.

In the supraventricular arrhythmia population, only 38 patients received doses greater than 600 mg bid, all of whom received 750 mg bid irrespective of creatinine clearance. In this very small patient population, the incidence of Torasemide de Pointes was 10.5% (4/38 patients), and the incidence of new ventricular tachycardia was 2.6% (1/38 patients).

TIKOSYN® Capsules

Table 8: Frequency of Adverse Events Occurring at >4% on TIKOSYN, and Numerically More Frequently on TIKOSYN than Placebo in Patients with Supraventricular Arrhythmias

<table>
<thead>
<tr>
<th>TIKOSYN</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>14.5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.8%</td>
</tr>
<tr>
<td>Torsade de Points</td>
<td>12.3%</td>
</tr>
<tr>
<td>Total</td>
<td>14.8%</td>
</tr>
</tbody>
</table>

**Adverse Events**

• Torsade de Pointes 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 QT interval must be individually calculated according to the calculated creatinine clearance and the QT interval should be used if the heart rate is <60 beats per minute. There are no data on use of QTc correction in patients with a heart rate >60 beats per minute. The usual recommended dose of TIKOSYN is 500 mg 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 significant bradycardia should be anticoagulated according to usual medical practice prior to electrical or pharmacological cardioversion. Antiarrhythmic 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 are to be discharged on TIKOSYN therapy from an inpatient setting as described above only after it has been ascertained that 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 subject to both 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 Individually 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 >440 milliseconds, or >500 in patients with ventricular arrhythmias, TIKOSYN is contraindicated. If heart rate is less than 60 beats per minute, QT interval should be used. Patients with heart rates <60 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:

creatinine clearance (male) = (140 – age) × actual body weight in kg

creatinine clearance (female) = (140 – age) × actual body weight in kg × 0.85

When serum creatinine is given in µmol/L, divide the value by 88.4 (1 mL = 88.4 µmol/L).

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

- Severe renal dysfunction (creatinine clearance <30 mL/min):
  - Dose: 250 mg twice daily
  - Adjust dose based on serum creatinine levels

- Moderate renal dysfunction (creatinine clearance 30-60 mL/min):
  - Dose: 500 mg twice daily
  - Adjust dose based on serum creatinine levels

- Normal renal function (creatinine clearance >60 mL/min):
  - Dose: 500 mg twice daily
  - Adjust dose based on serum creatinine levels

TIKOSYN® dose initiation is based on the QT interval, corrected for age and sex. It should be reduced by 25% if QTc is >440 ms.
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, if the QTc is greater than 500 msec (550 msec in patients with ventricular conduction abnormalities), subsequent dosing should be adjusted as follows:

<table>
<thead>
<tr>
<th>QTc Value</th>
<th>Adjusted Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than 440 msec</td>
<td>250 mcg twice daily</td>
</tr>
<tr>
<td>440–500 msec</td>
<td>250 mcg twice daily, 125 mcg twice daily</td>
</tr>
<tr>
<td>501–599 msec</td>
<td>125 mcg twice daily</td>
</tr>
<tr>
<td>600–799 msec</td>
<td>125 mcg once a day</td>
</tr>
</tbody>
</table>

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.

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:

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.

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 milliseconds 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 at TIKOSYN Therapy, Step 3.

Special Considerations

Consolidation of a Dose Lower than the 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 at 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 Torsade 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 this lower dose is increased, the patient needs to be rehospitalized for three days. Previous toleration of higher doses does not eliminate the need for rehospitalization.

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 Torsade 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 cardioversion 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 drugs(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 mcg) capsules are supplied as No. 4 capsules with a light orange cap and white body, printed with TKN 125 PFIZER, and are available in:

- Bottle of 60 0069-5800-60 0069-5810-60 0069-5820-60

TIKOSYN® 250 mcg (0.25 mcg) capsules are supplied as No. 4 capsules, peach cap and body, printed with TKN 250 PFIZER, and are available in:

- Bottle of 60 0069-5800-61 0069-5810-61 0069-5820-61

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


- Bottle of 60 0069-5800-63 0069-5810-63 0069-5820-63

Before taking TIKOSYN, tell your doctor about any 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.

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, TARKA)*
  - ketoconazole (NIZORAL, XOLEGEL, EXTINA)*
  - trimethoprim alone (PROLOPRIM, TRIMPEX)* or the combination of trimethoprim and sulfamethoxazole (BACTRIM, SEPTRA SULFATRIM)*
  - prochlorperazine (COMPazine, COMPO)*
  - megestrol (MEGACE)*
  - hydrochlorothiazide alone or in combination with other medicines (such as ESIDRIX, EZIDE, HYDRODIURIL, HYDRO-PAR, 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 list of these medicines.

- are pregnant or planning to become pregnant. It is not known if TIKOSYN will harm your unborn baby.

- 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.