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CLINICAL ALERT®

Dear Healthcare Professional,

At *MPR* we strive to bring you important drug information in a concise and timely fashion. In keeping with this goal, we are pleased to bring you this CLINICAL ALERT for TIKOSYN® (dofetilide) Capsules, from Pfizer Inc, highlighting important product information.

TIKOSYN, a Class III antiarrhythmic approved in 1999, is indicated for the maintenance of normal sinus rhythm (NSR) in patients with atrial fibrillation (AF) and atrial flutter (AFL) of greater than 1 week duration who have been converted to NSR and for the conversion of AF/AFL to NSR.[1] Reserve TIKOSYN for use in patients who have AF/AFL that is highly symptomatic, as it can cause life-threatening ventricular arrhythmias.[1] Additionally, 2 studies showed that TIKOSYN did not increase mortality in AF/AFL patients with structural heart disease and relatively high risk of sudden death vs placebo and was associated with reduced risk of hospitalization due to the worsening of congestive heart failure (CHF) in Class III/IV.[1-3]

As you may know, to prescribe TIKOSYN, the FDA requires prescriber certification. This requirement is part of the Risk Evaluation and Mitigation Strategy (REMS), intended to ensure the safe use of TIKOSYN and to mitigate the risk of induced arrhythmia. For additional information about certification, please visit www.TIKOSYNPro.com.

More information about the use of TIKOSYN is available at www.TIKOSYNPro.com.

Please see the accompanying TIKOSYN full Prescribing Information, including Boxed Warning, Medication Guide, and Important Safety Information.

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.

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.

(Important Safety Information on next page)

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

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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 reevaluated 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 the TIKOSYN full Prescribing Information, including Boxed Warning, and Medication Guide.

Sincerely,

Madonna Krawczyk, PharmD
Director of Clinical Communications
MPR Custom Programs

REFERENCES

1. Tikosyn [prescribing information]. New York, NY: Pfizer Inc; 2011. **2.** Køber L, Bloch-Thomsen PE, Møller M, et al; Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) Study Group. Effect of dofetilide in patients with recent myocardial infarction and left-ventricular dysfunction: a randomised trial. *Lancet*. 2000;356(9247):2052-2058. **3.** Torp-Pedersen C, Møller M, Bloch-Thomsen PE, et al; Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. *N Engl J Med*. 1999;341(12):857-865.

TIKOSYN®

(dofetilide) Capsules

℞

Also available in 250 mcg and 500 mcg

Company: Pfizer Inc
Pharmacologic Class: Class III antiarrhythmic.
Active Ingredient: Dofetilide
Indications:

- Maintenance of normal sinus rhythm in highly symptomatic patients with atrial fibrillation or atrial flutter of >1 week duration who were converted to normal sinus rhythm (use only for highly symptomatic patients)
- Conversion of atrial fibrillation and atrial flutter to normal sinus rhythm

Contraindications: Long QT syndromes. Baseline QT interval or QTc >440 msec (500 msec in ventricular conduction abnormalities). Severe renal impairment (creatinine clearance [CrCl] <20 mL/min). Concomitant cimetidine, verapamil, ketoconazole, trimethoprim (alone or in combination with sulfamethoxazole), hydrochlorothiazide (alone or in combination with triamterene), or inhibitors of renal cationic secretion (eg, prochlorperazine, megestrol). Patients with known hypersensitivity to TIKOSYN.

Warnings/Precautions: Initiate only in appropriate clinical setting; continue monitoring for at least 3 days. Individualize dose based on CrCl and QT interval (if heart rate <60 beats/minute). Risk of ventricular arrhythmias, especially torsade de pointes; monitor QTc, renal function (do baseline CrCl) at least every 3 months, and all concomitant drugs (including OTC drugs, herbs, supplements). Not been shown to be effective in paroxysmal atrial fibrillation. Not studied in HR <50 beats/min, sick sinus syndrome, 2nd- or 3rd-degree heart block (unless paced), severe hepatic impairment. Maintain normal potassium levels. Watch for conditions affecting electrolyte levels.

Interactions: See Contraindications. Stop dofetilide for at least 2 days before starting an interacting drug. Drugs that prolong QT interval (eg, phenothiazines, cisapride, bepridil, tricyclic antidepressants, some macrolides, and some fluoroquinolones): not recommended. Caution with drugs that undergo renal cationic secretion (eg, triamterene, metformin, amiloride) and with CYP3A4 inhibitors (eg, macrolides, azole antifungals, protease inhibitors, SSRIs, amiodarone, cannabinoids, diltiazem, grapefruit juice, nefazodone, norfloxacin, quinine, zafirlukast); these may increase dofetilide levels. Allow at least 3 half-lives to elapse and monitor when withdrawing Class I or III antiarrhythmics before giving 1st dose of dofetilide; reduce serum amiodarone levels to <0.3 mg/L or withdraw at least 3 months before starting dofetilide. Potassium-depleting diuretics, digoxin may increase risk of torsade de pointes.

Special Populations: Pediatrics: <18 yrs: not recommended. Pregnancy (Category C). Nursing mothers: not recommended.

Adverse Reactions: Most common include headache, chest pain, dizziness, respiratory tract infection, dyspnea, nausea.

How Supplied: Caps: 125 mcg, 250 mcg, 500 mcg—Bottle of 14 and 60.

A Vaughan Williams Class III antiarrhythmic in clinical use for more than 10 years[1,2]

- TIKOSYN is indicated for
  - Maintenance of normal sinus rhythm (NSR) in patients with highly symptomatic atrial fibrillation (AF) and atrial flutter (AFL) of >1 week duration who were converted to NSR[1]
  - Conversion of highly symptomatic AF/AFL to NSR[1]

Important Safety Information

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Clinically shown to maintain and convert patients with AF or AFL to NSR[1]

- Two randomized, parallel, double-blind, placebo-controlled, dose-response studies evaluated TIKOSYN® (dofetilide) for its ability to convert patients with AF/AFL to NSR[1]
  - A total of 996 patients with a 1-week to 2-year history of AF/AFL were enrolled[1]
  - Both studies randomized patients to placebo or to doses of TIKOSYN 125 mcg, 250 mcg, 500 mcg, or (in one study) a comparator drug, given twice a day (these doses were lowered based on calculated creatinine and, [in one study] for QT interval or QTc)[1]
- TIKOSYN was shown to
  - Maintain NSR after drug-induced or electrical cardioversion (**Figure 1**)[1]
  - Convert patients with AF or AFL of >1 week duration to NSR[1]

Figure 1

PROBABILITIES OF TIKOSYN PATIENTS REMAINING AT NSR AT 6 AND 12 MONTHS

	250 mcg BID	500 mcg BID	Placebo
6 months	53.9%	67.5%	30.3%
12 months	46.9%	63%	22.5%

In two randomized parallel, double-blind, placebo-controlled, dose-response studies (number of patients evaluated for maintenance of NSR: 503 TIKOSYN, 174 placebo).

Source: Data on file.[3]

Did not incease mortality and reduced risk of hospitalizations associated with congestive heart failure[1,4,5]

- The DIAMOND studies (The Danish Investigations of Arrhythmia and Mortality on Dofetilide) were 3-year trials comparing the effects of TIKOSYN and placebo on mortality and morbidity in patients with impaired left ventricular (LV) function (ejection fraction ≤35%)[1,4,5]
  - One study was in patients with moderate to severe (60% NYHA Class III or IV) congestive heart failure (DIAMOND-CHF; N=1518)[1]
  - The second study was in patients with recent myocardial infarction (DIAMOND-MI; N=1510), of whom 40% had NYHA Class III or IV heart failure[1]
  - Both groups were at relatively high risk of sudden death[1]
  - The DIAMOND trials were intended to determine whether TIKOSYN could reduce the risk of sudden death[1]
- Results of the 2 DIAMOND studies showed
  - TIKOSYN did not increase mortality in AF or AFL patients with structural heart disease [SHD] and relatively high risk of sudden death vs placebo[1,4]
  - TIKOSYN reduced risk of hospitalization due to worsening of congestive heart failure (CHF) in Class III or IV CHF patients (risk ratio: 0.75; 95% CI: 0.63-0.89) in one of the 2 studies[5]

Important Safety Information

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Is TIKOSYN® (dofetilide) an option for your highly symptomatic AF/AFL patients with concomitant mild to moderate hepatic impairment?

CASE STUDY 1*

Steve is a 71-year-old male seeking treatment for his recurring severe symptoms of AF

Past Medical History
- Hyperlipidemia
- Hypertension
- History of MI
- CAD with stents in LAD and circumflex coronary arteries
- Nonalcoholic fatty liver disease (NAFLD)

Current Medications
- ACEI
- Beta-blocker
- Statin
- Warfarin

Treatment Decision
- Steve has elevated LFTs due to a history of NAFLD in addition to his AF symptoms
- Antiarrhythmic options include TIKOSYN, as it may be used in patients with concomitant mild to moderate hepatic impairment
- Steve will be started on TIKOSYN 500 mcg BID and will continue with maintenance therapy for his highly symptomatic AF

Physical Exam

Resting Pulse
78 BPM, regular

BP
130/70 mm Hg

Laboratory Results

CrCl
74 mL/min

AST
70 U/L

ALT
131 U/L

Lipid Panel
TC: 190 mg/dL
TG: 147 mg/dL
HDL: 53 mg/dL
LDL: 92 mg/dL

ECG Results
Normal sinus rhythm

ACEI = angiotensin-converting enzyme inhibitor; CAD = coronary artery disease; LAD = left anterior descending; LFT = liver function test; MI = myocardial infarction.

**This hypothetical case study is presented only as an example. It is not intended to instruct any healthcare provider in the treatment of any illness nor is it meant to substitute for medical training or to be relied upon in treating any individual patient.*

Important Safety Information (*continued*)

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.

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Please see full Prescribing Information, including Boxed Warning, and Medication Guide for TIKOSYN.

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Is TIKOSYN® (dofetilide) an option for your highly symptomatic AF/AFL patients with SHD and/or CHF?

CASE STUDY 2*

Mark is a 69-year-old post-MI patient with class II chronic CHF who presents with highly symptomatic AF

Past Medical History
- History of MI
- CHF, class III
- Hypertension

Current Medications
- ACEI
- Beta-blocker
- Furosemide
- Dabigatran

Treatment Decision
- Mark is currently hospitalized for a new onset of highly symptomatic AF associated with CV risk factors and is currently taking dabigatran
- TIKOSYN is recommended as a first-line treatment option for sinus rhythm maintenance in patients with heart failure in the ACCF/AHA/HRS guidelines[6]
- Following stabilization on anticoagulation agents, Mark will be started on TIKOSYN 500 mcg BID

Physical Exam

Resting Pulse
110 BPM, irregular

BP
142/88 mm Hg

Laboratory Results

CrCl
72 mL/min

ECHO
LVEF = 33%

ECG Results
Irregular rhythm
- QRS duration: 96 ms
- QT/QTc: 322 ms/436 ms

ACCF = American College of Cardiology Foundation; ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; AHA = American Heart Association; BPM = beats per minute; CHF = chronic heart failure; CV = cardiovascular; ECHO = echocardiogram; HRS = Heart Rhythm Society; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; MI = myocardial infarction; SHD = structural heart disease.

**This hypothetical case study is presented only as an example. It is not intended to instruct any healthcare provider in the treatment of any illness nor is it meant to substitute for medical training or to be relied upon in treating any individual patient.*

Important Safety Information (*continued*)

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

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.

Please see full Prescribing Information, including Boxed Warning, and Medication Guide for TIKOSYN.

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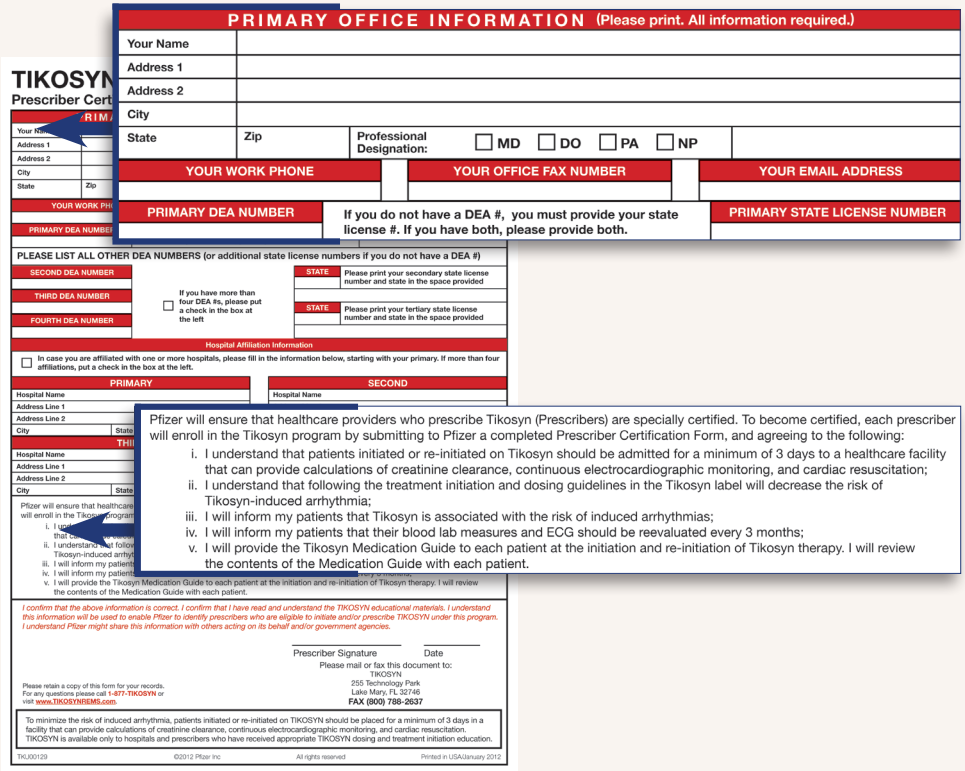
Prescriber Certification for TIKOSYN® (dofetilide)

- [✓] **To prescribe TIKOSYN, certification is required**
  - A one-time recertification is required for prescribers certified prior to July 2011
- [✓] **Complete the program by visiting www.TIKOSYNREMS.com**
  - Review the TIKOSYN Treatment Guidelines, Prescribing Information, and Medication Guide
  - Complete the Prescriber Certification Form (**included**), and fax it to **1-800-788-2637**
- [✓] **Upon receipt of the Prescriber Certification Form, your name will be added to the TIKOSYN prescriber list**
  - Confirm your certification after 1 to 2 business days by calling **1-866-249-7261**
  - A written confirmation will be sent to you upon receipt of your certification form
- [✓] **Certified pharmacies can fill prescriptions for TIKOSYN written only by certified prescribers**

PRESCRIBER CERTIFICATION FORM



PRIMARY OFFICE INFORMATION (Please print. All information required.)

Your Name			
Address 1			
Address 2			
City			
State	Zip	Professional Designation: ☐ MD ☐ DO ☐ PA ☐ NP	

YOUR WORK PHONE	YOUR OFFICE FAX NUMBER	YOUR EMAIL ADDRESS

PRIMARY DEA NUMBER		PRIMARY STATE LICENSE NUMBER
	If you do not have a DEA #, you must provide your state license #. If you have both, please provide both.	

TIKOSYN
Prescriber Cert

PLEASE LIST ALL OTHER DEA NUMBERS (or additional state license numbers if you do not have a DEA #)

SECOND DEA NUMBER	If you have more than four DEA #s, please put a check in the box at the left ☐	STATE — Please print your secondary state license number and state in the space provided
THIRD DEA NUMBER		STATE — Please print your tertiary state license number and state in the space provided
FOURTH DEA NUMBER		

Hospital Affiliation Information

☐ In case you are affiliated with one or more hospitals, please fill in the information below, starting with your primary. If more than four affiliations, put a check in the box at the left.

PRIMARY	SECOND
Hospital Name	Hospital Name
Address Line 1	
Address Line 2	
City State	

Pfizer will ensure that healthcare providers who prescribe Tikosyn (Prescribers) are specially certified. To become certified, each prescriber will enroll in the Tikosyn program by submitting to Pfizer a completed Prescriber Certification Form, and agreeing to the following:

i. I understand that patients initiated or re-initiated on Tikosyn should be admitted for a minimum of 3 days to a healthcare facility that can provide calculations of creatinine clearance, continuous electrocardiographic monitoring, and cardiac resuscitation;
ii. I understand that following the treatment initiation and dosing guidelines in the Tikosyn label will decrease the risk of Tikosyn-induced arrhythmia;
iii. I will inform my patients that Tikosyn is associated with the risk of induced arrhythmias;
iv. I will inform my patients that their blood lab measures and ECG should be reevaluated every 3 months;
v. I will provide the Tikosyn Medication Guide to each patient at the initiation and re-initiation of Tikosyn therapy. I will review the contents of the Medication Guide with each patient.

I confirm that the above information is correct. I confirm that I have read and understand the TIKOSYN educational materials. I understand this information will be used to enable Pfizer to identify prescribers who are eligible to initiate and/or prescribe TIKOSYN under this program. I understand Pfizer might share this information with others acting on its behalf and/or government agencies.

Prescriber Signature _____ Date _____

Please mail or fax this document to:
TIKOSYN
255 Technology Park
Lake Mary, FL 32746
FAX (800) 788-2637

Please retain a copy of this form for your records.
For any questions please call 1-877-TIKOSYN or visit www.TIKOSYNREMS.com.

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.

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Please see full Prescribing Information, including Boxed Warning, and Medication Guide for TIKOSYN.

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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.

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

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REFERENCES

1. Tikosyn [prescribing information]. New York, NY: Pfizer Inc; 2011. **2.** US Department of Health and Human Services. Drug Details. Drugs@FDA Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. Accessed July 7, 2011. **3.** Data on file. TIKOSYN NDA 20-931 3-9-1998. Pfizer Inc. **4.** Køber L, Bloch-Thomsen PE, Møller M, et al; Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) Study Group. Effect of dofetilide in patients with recent myocardial infarction and left-ventricular dysfunction: a randomised trial. *Lancet*. 2000;356(9247):2052-2058. **5.** Torp-Pedersen C, Møller M, Bloch-Thomsen PE, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. *N Engl J Med*. 1999;341(12):857-865. **6.** Wann LS, Curtis AB, January CT, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;123(1):104-123.

TKU00188D/TKU495702-01 9/12