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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 safety and efficacy data.

As you may know, TIKOSYN can only be prescribed by a certified TIKOSYN prescriber. If you are not already certified, but interested in becoming a TIKOSYN prescriber, you must first complete the TIKOSYN Education Program. This program provides comprehensive education about the importance of in-hospital treatment initiation and individualized dosing. Visit www.tikosyn.com for more information on how to become a certified TIKOSYN prescriber.

TIKOSYN, a Class III antiarrythmic approved in 1999, is indicated for the conversion of atrial fibrillation (AF) and atrial flutter (AFl) to normal sinus rhythm (NSR) and for maintenance of NSR in patients with AF/AFl of greater than 1 week duration who have been converted to NSR.[1] Because TIKOSYN can cause life-threatening ventricular arrhythmias, it should be reserved for patients in whom AF/AFl is highly symptomatic.[1]

In clinical trials, TIKOSYN has converted and maintained patients in NSR.[1] TIKOSYN has been in clinical use for more than 10 years.

More information about the use of TIKOSYN is available on the *MPR* Web site at www.eMPR.com and at www.tikosyn.com.

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

Sincerely,

Grace L. McBride
Editorial Director
MPR Custom Programs

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.

(Important Safety Information continued on next page)

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.

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.

REFERENCE

1. TIKOSYN [package insert]. New York, NY: Pfizer Inc; 2006.

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CLINICAL ALERT

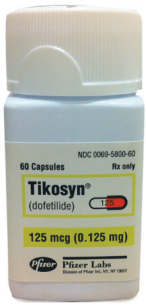
TIKOSYN®

(dofetilide) Capsules

Company: Pfizer Inc ℞
Pharmacologic Class: Class III antiarrhythmic
Active Ingredient: Dofetilide
Indications: Maintenance of normal sinus rhythm in 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.
Adults: ≥18yrs: 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). Recommended dose: 500 mcg BID. See Prescribing Information for individualized dose initiation and additional dosing information.
Children: <18yrs: not recommended
Contraindications: Long QT syndromes. Baseline QT interval or QTc >440 msec (500 msec in ventricular conduction abnormalities). Severe renal impairment (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).

WARNING: Risk of induced arrhythmia. Continuously monitor cardiac and renal function of initiated/re-initiated patients for at least 3 days in medical facility.

Warnings/Precautions: 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). Paroxysmal atrial fibrillation. Heart rate <50 beats/minute. Sick sinus syndrome. 2nd- or 3rd-degree heart block, unless paced. Renal or severe hepatic impairment. Maintain normal potassium levels. Conditions affecting electrolyte levels. Pregnancy (Cat.C). Nursing mothers: not recommended.
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 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.
Adverse Reactions: (>2%) Headache, chest pain, dizziness, respiratory tract infection, dyspnea, nausea, flu syndrome, insomnia, back pain, diarrhea, rash, abdominal pain, torsade de pointes, serious ventricular arrhythmias, conduction disturbances.
How Supplied: Caps: 125 mcg, 250 mcg, 500 mcg—14, 60



Also available in 250 mcg and 500 mcg

TIKOSYN is indicated for

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

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

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☑ Efficacy evaluated in two large multicenter trials (EMERALD* and SAFIRE-D†)

- Randomized, parallel, double-blind, placebo controlled, dose-response trials evaluated[1]
  - – Ability to convert patients with AF/AFl of >1 week's duration to NSR[1]
  - – Ability to maintain NSR (delay time to recurrence of AF/AFl) after drug-induced or electrical cardioversion for up to 12 months[1]

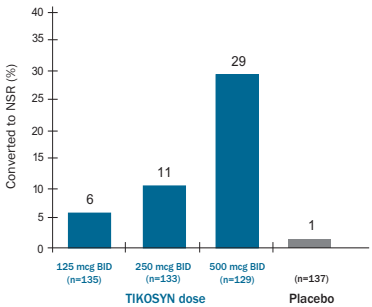
☑ EMERALD showed TIKOSYN was significantly more effective than placebo in patient conversion‡ to NSR

- Patients who remained in NSR after in-hospital conversion were continued on randomized therapy as outpatients for up to 1 year unless they experienced AF/AFl recurrence[1]
- TIKOSYN was more efficacious at 500 mcg twice daily dose, resulting in a conversion rate of 29% vs 1% with placebo (**Figure 1**)[1]

Figure 1

EMERALD

Pharmacologic Conversion Increases With Increasing Doses of TIKOSYN



The chart above represents patients randomized to TIKOSYN 125 mcg BID (n=135), 250 mcg BID (n=133), 500 mcg BID (n=129), or placebo (n=137). Conversion was defined as maintenance of NSR for at least 1 hour and still in NSR on day 3.

Source: Package insert.[1]

☑ TIKOSYN was significantly more effective than placebo in maintaining patients in NSR at 12 months[1]

- There was a 71% probability of maintaining NSR at 6 months with TIKOSYN 500 mcg twice daily vs 26% with placebo[1]
- There was a 66% probability of maintaining NSR at 12 months with TIKOSYN 500 mcg twice daily vs 21% with placebo (P=.0001)[1]

*EMERALD = European and Australian Multicenter Evaluative Research on Atrial Fibrillation and Dofetilide.

†SAFIRE-D = Symptomatic Atrial Fibrillation Investigative Research on Dofetilide.

‡Conversion defined as maintenance of NSR for at least 1 hour and still in NSR on day 3.

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In SAFIRE-D, TIKOSYN was significantly more effective in converting patients to NSR compared to placebo[2,§]

- TIKOSYN 500 mcg twice daily resulted in a conversion rate of 29.9% vs 1.2% with placebo ($P<.001$) (**Figure 2**)[2]

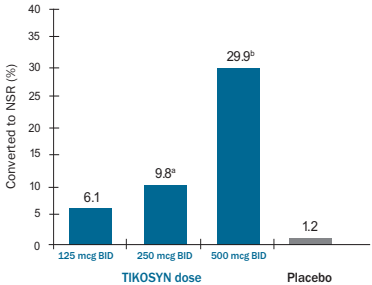
At 12 months, 500 mcg twice daily of TIKOSYN was most effective in maintaining NSR[2]

- At 6 months, there was a 62% probability of maintaining NSR with TIKOSYN compared to 37% with placebo[1]
- At 12 months, there was a 58% probability of maintaining NSR with TIKOSYN compared to 25% with placebo ($P<.001$)[1]

Figure 2

SAFIRE-D

Pharmacologic Conversion Increases With Increasing Doses of TIKOSYN



In SAFIRE-D, conversion was defined as maintenance of NSR for at least 24 hours. The percentages of patients converted to NSR are displayed for each treatment group.

[a]$P=.015$ vs placebo.
[b]$P<.001$ vs placebo.

Source: Singh 2000.[2]

The DIAMOND¶ Studies showed that TIKOSYN does not increase mortality in patients with structural heart disease[1]

- Two 3-year trials compared the effects of TIKOSYN 500 mcg twice daily vs placebo on mortality and morbidity in patients with impaired left ventricular function[1]
  - The DIAMOND-MI study showed the probability of survival at 1 year was 79% in the TIKOSYN group vs 77% placebo ($P=.23$) in patients with recent myocardial infarction[1,3]
  - The DIAMOND-CHF study showed the probability of survival at 1 year was 73% in the TIKOSYN group vs 72% placebo ($P=.54$) in patients with congestive heart failure[1,4]
- A subanalysis was conducted in patients with AF receiving TIKOSYN 250 mcg twice daily in the DIAMOND trials[1]
  - Results showed that TIKOSYN use was not associated with excess risk of mortality[1]

§Conversion defined as achieving and maintaining NSR for at least 24 hours.

¶DIAMOND = The Danish Investigations of Arrhythmias and Mortality on Dofetilide.

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REFERENCES

1. TIKOSYN [package insert]. New York, NY: Pfizer Inc; 2006. **2.** Singh S, Zoble RG, Yellen L, et al. Efficacy and safety of oral dofetilide in converting to and maintaining sinus rhythm in patients with chronic atrial fibrillation or atrial flutter: the symptomatic atrial fibrillation investigative research on dofetilide (SAFIRE-D) study. *Circulation*. 2000;102(19):2385-2390. **3.** Køber L, Bloch-Thomsen PE, Møller M, et al; for the 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. **4.** Torp-Pedersen C, Møller M, Bloch-Thomsen PE, et al; for the 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.

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