

TIKOSYN® (dofetilide) TREATMENT GUIDELINES

These guidelines are part of the TIKOSYN Risk Evaluation and Mitigation Strategy (REMS) program. Prescribers and Pharmacists are required to read these guidelines and sign a Certification Form acknowledging they understand the potential risks of TIKOSYN in order to prescribe and dispense TIKOSYN.

Below, you will find detailed treatment guidelines for TIKOSYN[®] (dofetilide). Please call 1-877-TIKOSYN if you need additional information.

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Important Safety Information

TIKOSYN is indicated for the conversion and maintenance of normal sinus rhythm (delay in the time to recurrence of atrial fibrillation/atrial flutter) in highly symptomatic patients with atrial fibrillation/atrial flutter of greater than 1 week.

TIKOSYN is contraindicated with verapamil, with hydrochlorothiazide (alone or in combinations such as with triamterene), and with cation transport inhibitors such as cimetidine, ketoconazole, trimethoprim (alone or in combination with sulfamethoxazole), prochlorperazine, and megestrol. (Alternatives to cimetidine include Maalox®, Prilosec®, and Zantac®.)

Warnings/Interactions: Inhibitors of the CYP3A4, renal cation transports, drugs that prolong the QT interval, and other antiarrhythmics may increase the risk of proarrhythmia either by increasing dofetilide exposure or by adding to its QT-prolonging effect.

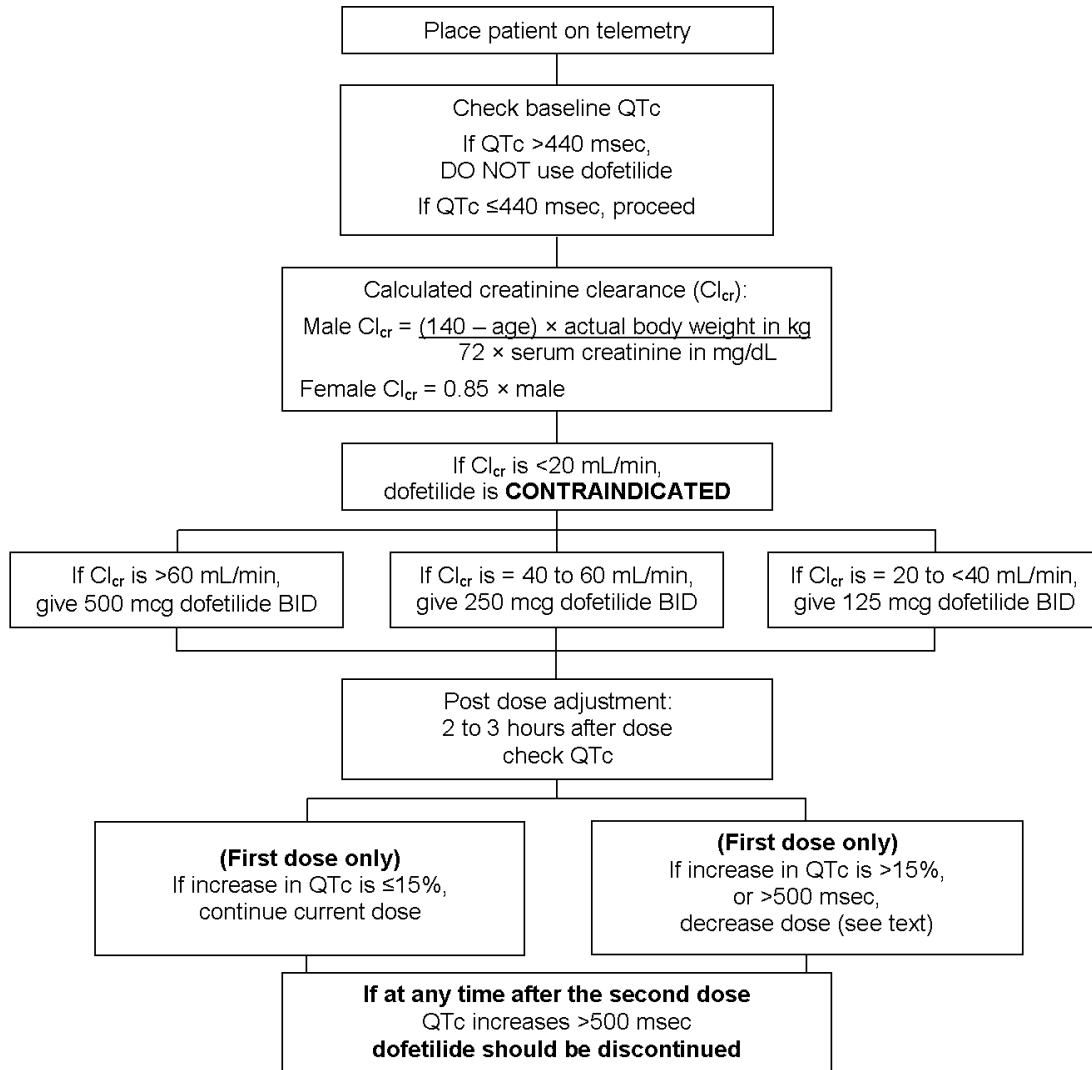
Precautions/Interactions: The following should be coadministered with care as they might increase dofetilide levels: macrolide antibiotics, azole antifungal agents, protease inhibitors, selective serotonin reuptake inhibitors, amiodarone, cannabinoids, diltiazem, nefazodone, zafirlukast, norfloxacin, quinine, triamterene, metformin, amiloride, and grapefruit juice.

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.

Dosing Overview

Please review this overview of dosing for TIKOSYN® (dofetilide).

Dosing Algorithm Used in the TIKOSYN Clinical Program



TIKOSYN [product information] New York, NY; Pfizer Inc.: 2004

Steps for Initiation and Dosing

The following are suggested guidelines for the initiation and dosing of TIKOSYN[®] (dofetilide).

PREDOSE STEPS

1. Before initiating TIKOSYN therapy, previous antiarrhythmic therapy should be withdrawn for a minimum of 3 plasma half-lives. TIKOSYN should not be initiated following amiodarone therapy until amiodarone plasma levels are below 0.3 mcg/mL or until amiodarone has been withdrawn for at least 3 months.
2. Patients with atrial fibrillation should be anticoagulated according to usual medical practice.
3. Admit patient to the telemetry unit; choose a telemetry lead with a visible QT interval. All measurements of the QT interval should be from this lead.
4. Telemetry monitoring should continue for a minimum of 3 days or for 12 hours after conversion to normal sinus rhythm, whichever is longer.
5. The concomitant use of verapamil, hydrochlorothiazide (alone or in combination, such as with triamterene), or the cation transport system inhibitors cimetidine, trimethoprim (alone or in combination with sulfamethoxazole), and ketoconazole with TIKOSYN is contraindicated, as each drug causes a substantial increase in dofetilide plasma concentration. In addition, other known inhibitors of the renal cation transport system, such as prochlorperazine and megestrol, should not be used in patients on TIKOSYN. Please see full prescribing information for TIKOSYN.
6. **CAUTION should be used when coadministering TIKOSYN with macrolide antibiotics, azole antifungals, protease inhibitors, and SRIs, as these agents may increase blood levels of TIKOSYN.**
7. Concomitant administration of TIKOSYN and digoxin is permitted. Carefully monitor patients for the signs and symptoms of digoxin toxicity. The concomitant administration of digoxin was associated with a higher occurrence of torsades de pointes. It is not clear whether this represents an interaction with TIKOSYN or the presence of more severe structural heart disease in patients taking digoxin.
8. If potassium (K⁺) is <4.0 mEq/L, replace K⁺ before administration of TIKOSYN.
9. Before administering the first dose of TIKOSYN on Day 1, measure the QTc interval (determine the QT if the heart rate is <60 bpm or >100 bpm).
 - If baseline QTc is >440 msec (500 msec in patients with ventricular conduction abnormalities), TIKOSYN is **CONTRAINDICATED**; if ≤440 msec, you may proceed.
 - Note time, date, and the telemetry lead on the strip.
 - All measurements of the QTc interval should be from this lead.
10. Measure the QT interval (determine QTc) 2-3 hours after each dose of TIKOSYN until the patient is discharged.

11. Determine the patient's actual body weight in kg.
12. Measure patient's serum creatinine level as mg/dL.
13. Calculate patient's creatinine clearance using the following formula:

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

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

DOSING

14. The creatinine clearance results should be received by the pharmacy to dispense the first TIKOSYN[®] (dofetilide) dose.

15. If the calculated creatinine clearance is <20 mL/min, TIKOSYN is **CONTRAINDICATED**.

16. If the calculated creatinine clearance is >60 mL/min, the appropriate dose of TIKOSYN is 500 mcg BID.

- 2-3 hours after the **initial dose**, if QTc increases to >15% from baseline, then decrease TIKOSYN to 250 mcg BID.

17. If the calculated creatinine clearance is between 40 mL/min and 60 mL/min, the appropriate dose of TIKOSYN is 250 mcg BID.

- 2-3 hours after the **initial dose**, if QTc increases to >15% from baseline, then decrease TIKOSYN to 125 mcg BID.
- If QTc increases to >500 msec (550 msec in the presence of a ventricular conduction abnormality), TIKOSYN should be decreased to 125 mcg BID.

18. If the calculated creatinine clearance is 20 mL/min to <40 mL/min, the appropriate dose of TIKOSYN is 125 mcg BID.

- >2-3 hours after the **initial dose**, if QTc increases to >15% from baseline, then decrease TIKOSYN to 125 mcg QD.
- If QTc increases to >500 msec (550 msec in the presence of a ventricular conduction abnormality), then decrease TIKOSYN to 125 mcg QD.

POSTDOSE ADJUSTMENTS

19. The **second dose** of TIKOSYN should only be given after the QT has been determined. Only 1 down titration of TIKOSYN for QTc is suggested. If QTc is still excessively prolonged, DISCONTINUE TIKOSYN therapy.

20. During therapy initiation in the hospital, at 2-3 hours after each dose of TIKOSYN, determine the QTc to see if dose adjustment is necessary.

- Response to QT measurement after the **first dose**:
 - If QTc increases by >15% or is >500 msec (550 msec in the presence of a ventricular conduction abnormality), decrease the TIKOSYN[®] (dofetilide) dose as described above.
- Response to QT measurement after **subsequent doses**:
 - If after subsequent doses the QTc is >500 msec (550 msec in the presence of a ventricular conduction abnormality), TIKOSYN should be DISCONTINUED.

21. TIKOSYN should be given q12h (actual times may vary according to local hospital practice; the doses should be given at the same time each day, ie, 12 hours apart); QD TIKOSYN should be given at the same time every day. The risk of torsades de pointes is related to dose as well as to patient characteristics. Physicians may, therefore, in some cases, choose doses lower than determined by the algorithm. If at any time this lower dose is increased, the patient needs to be rehospitalized for 3 days. Previous toleration of higher doses does not eliminate the need for rehospitalization.

22. After the third TIKOSYN dose, discuss with patient the option of filling Rx with patient's mail-order or retail pharmacy. Both the mail-order and retail pharmacy must be enrolled in the T.I.P.S. program. The physician who orders a TIKOSYN prescription must be a confirmed participant of a TIKOSYN education program. You will need the patient's final dose of TIKOSYN, patient's full name (correct spelling), address, insurer, and physician's name. If the TIKOSYN dose is changed or discontinued after the prescription has been faxed, please notify the mail-order or retail pharmacy immediately.

The T.I.P.S.[™] Program is designed to allow retail pharmacies to stock and dispense TIKOSYN once they have been enrolled. Please visit www.TIKOSYNREMS.com for T.I.P.S.[™] enrollment information.

23. Contact your hospital pharmacy to order a TIKOSYN bottle with 14 capsules of the final dosage strength.* The patient should be discharged with this bottle to ensure a sufficient drug supply for uninterrupted dosing until the patient receives the first outpatient supply of medication. Patient will be directed to fill prescription as soon as possible, since pharmacy may not have TIKOSYN stocked and requires at least 24 hours to fill prescription.

*This bottle is supplied free of charge to hospitals.

ACTIONS PRIOR TO PATIENT DISCHARGE

24. Ensure the patient received the TIKOSYN discharge bottle with 14 capsules.

25. Review the Medication Guide with your patient.

26. Alert patients that blood work and ECG will be re-evaluated every 3 months by their doctor to check the renal function and the QTc.

- If QTc exceeds 500 msec (550 msec in patients with ventricular conduction abnormalities), TIKOSYN therapy should be discontinued and patients should be carefully monitored until QTc returns to baseline levels. If renal function deteriorates, adjust dose as described in steps 16-18 under "Dosing Overview."

27. Inform the patient's Healthcare Professional that the patient is now on TIKOSYN[®] (dofetilide). Important points to mention include:

- TIKOSYN is contraindicated with verapamil, hydrochlorothiazide (alone or in combination, such as with triamterene), and cation transport inhibitors such as cimetidine, ketoconazole, trimethoprim (alone or in combination with sulfamethoxazole), prochlorperazine, and megestrol.
- Renal function and QTc should be re-evaluated every 3 months or as medically warranted.
- TIKOSYN is available through a mail-order or retail pharmacy enrolled in the T.I.P.S. program. If the Healthcare Professional would like to write a refill for the patient, he or she must be a confirmed participant in a TIKOSYN REMS program before the mail-order or retail pharmacy can fill the prescription. The Healthcare Professional can learn how to do this by calling 1-877-TIKOSYN (845-6796). Alternatively, the Healthcare Professional can continue to see the patient in consultation with a physician who is a confirmed participant in a TIKOSYN REMS program.
- On receipt of patient information, the Healthcare Professional should read the enclosed package insert for more information. The most serious side effect of TIKOSYN is torsades de pointes. The most common side effects with TIKOSYN occurred at rates similar to placebo and included headache, chest pain, and dizziness.

Patient Counseling

28. Advise your patients to:

- Read the Medication Guide every time they receive their prescription, including refills
- Not take cimetidine, verapamil, ketoconazole, trimethoprim/sulfamethoxazole, hydrochlorothiazide, prochlorperazine, or megestrol
- Tell you of all medications they are taking including prescription, non-prescription, natural/herbal remedies, and vitamins or dietary supplements
- Report symptoms associated with electrolyte imbalance, including excessive or prolonged diarrhea, sweating, vomiting, or loss of appetite or thirst
- Not miss doses or take extra doses of TIKOSYN
- Not start any other medications, including OTCs without first consulting their doctor
- Get prescriptions filled and refilled as soon as possible to avoid any disruptions in treatment
- Report any adverse events

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For full prescribing information, please visit www.TIKOSYNREMS.com.