1. **NAME OF THE MEDICINAL PRODUCT**

TIKOSYN 125 microgram hard capsules

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each capsule contains 125 micrograms of dofetilide

3. **PHARMACEUTICAL FORM**

Capsules, hard

TIKOSYN 125 microgram capsules are orange and white and are marked with TKN 125 PFIZER

4. **CLINICAL PARTICULARS**

4.1 Therapeutic indications

Tikosyn is a Class III antiarrhythmic agent that is indicated for the following:

(i) Conversion of persistent atrial fibrillation or atrial flutter to normal sinus rhythm in patients in whom cardioversion by electrical means is not appropriate and in whom the duration of the arrhythmic episode is less than 6 months (see section 5.1).

(ii) Maintenance of sinus rhythm (after conversion) in patients with persistent atrial fibrillation or atrial flutter. Because TIKOSYN can cause ventricular arrhythmias, it should be reserved for patients in whom atrial fibrillation/atrial flutter is highly symptomatic and in whom other antiarrhythmic therapy is not appropriate.

Dofetilide has not been shown to be effective in patients with paroxysmal atrial arrhythmias (including paroxysmal atrial fibrillation).

4.2 Posology and Method of Administration

- During treatment with TIKOSYN, patients must be managed by a specialist experienced in the treatment of arrhythmias.
- Therapy with TIKOSYN must be initiated in an in-patient setting that provides continuous ECG monitoring. Patients should be monitored for at least the first three days (72 hours) of TIKOSYN therapy and for at least 12 hours after electrical or pharmacological conversion.
- TIKOSYN capsules can be taken with or without food.
- The dose of TIKOSYN must be individualised for every patient according to calculated creatinine clearance, cardiac status (see below) and QTc.

**Measurement of QT Interval:**

Prior to administration of the first dose, the QTc must be determined using an average of 5-10 beats. For patients with a heart rate greater than 60 beats per minute, QTc is calculated using Bazett’s formula as follows: QTc = QT / √RR. However, if the heart rate is less than 60 bpm, QT (not QTc) interval should be used. If the QTc (or QT interval as appropriate) is greater
than 440 msec (or 500 msec in patients with ventricular conduction abnormalities), TIKOSYN is contraindicated.

**Calculation of Creatinine Clearance**

Prior to the administration of the first dose the patient’s creatinine clearance must be calculated. This is calculated from serum creatinine (μmol/l) using the following formula:

\[
\text{creatinine clearance} \ (\text{male}) = \frac{(140-\text{age}) \times \text{body weight in kg} \times 1.22}{\text{serum creatinine} \ (\mu\text{mol/l})} \ \text{ml/min}
\]

\[
\text{creatinine clearance} \ (\text{female}) = \frac{(140-\text{age}) \times \text{body weight in kg} \times 1.04}{\text{serum creatinine} \ (\mu\text{mol/l})} \ \text{ml/min}
\]

When serum creatinine is in mg/dl, the calculated value obtained must be multiplied by 88.4 (1 mg/dl = 88.4 μmol/l) to determine the creatinine clearance.

**Dose regimen**

- The maximum recommended dose is 500 micrograms twice daily for patients with normal renal function and normal cardiac status. Patients with symptomatic heart failure or recent myocardial infarction (MI), with left ventricular dysfunction (ejection fraction (EF) ≤ 35%) should **not** receive doses in excess of 250 micrograms twice daily.
- TIKOSYN must only be dosed according to the flow chart, taking into account the patient’s baseline QTc, creatinine clearance and cardiac status (see below).

**Starting dose for conversion and maintenance**

TIKOSYN is contraindicated when the baseline QTc interval is >440 msec.

In patients with baseline QTc ≤ 440 msec, the starting dose of TIKOSYN is summarised below and is detailed in the following flow chart:

<table>
<thead>
<tr>
<th>Calculated creatinine clearance:</th>
<th>Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with symptomatic CHF or recent MI with ejection fraction ≤ 35%</td>
<td>Other patients</td>
</tr>
<tr>
<td>&gt; 60 ml/min</td>
<td>250 micrograms twice daily</td>
</tr>
<tr>
<td>&gt;40≤60 ml/min</td>
<td>250 micrograms twice daily</td>
</tr>
<tr>
<td>≥20≤40 ml/min</td>
<td>125 micrograms twice daily</td>
</tr>
<tr>
<td>&lt; 20 ml/min</td>
<td>Dofetilide is contraindicated in these patients.</td>
</tr>
</tbody>
</table>
Place Patient on continuous ECG monitoring

Check baseline QTc
If QTc >440msec, do not use TIKOSYN
If QTc ≤ 440msec, proceed

Calculate creatinine clearance (CLcr)

If CLcr <20 ml/min,
dofetilide is
CONTRAINDICATED

If CLcr is >60 ml/min,
assess cardiac status

If patients have
symptomatic
CHF or recent
MI, with EF
≤ 35%, start
with 250
micrograms
twice daily

If CLcr is = 40-60 ml/min,
start with 250 micrograms
dofetilide twice daily

If CLcr is = 20-<40 ml/min,
start with 125 micrograms
dofetilide twice daily

For other
patients start
with 500
micrograms
twice daily

2-3 hours after the first dose check the QTc

(Post first dose only)
If increase in QTc is ≤15%,
continue current dose

(Post first dose only)
If increase in QTc is >15%
or QTc is >500 msec,
Decrease The Dose:
if 500 micrograms BID, reduce to 250 micrograms BID
if 250 micrograms BID, reduce to 125 micrograms BID
if 125 micrograms BID, reduce to 125 micrograms OD

QTc must be determined 2-3 hours after each in-patient dose.
If at any time after the second dose QTc increases above 500 msec dofetilide should be discontinued
Special Considerations

Switch to TIKOSYN capsules from Class I or other Class III antiarrhythmic therapy
Before initiating TIKOSYN capsules, previous Class I or Class III antiarrhythmic therapy should be withdrawn for a minimum of 3 plasma half-lives. Due to the unpredictable pharmacokinetics of amiodarone, TIKOSYN capsules should not be initiated following amiodarone therapy until amiodarone plasma levels are below 0.3 μg/ml or after amiodarone has been withdrawn for three months.

Cardioversion
The minimum monitoring period after initiation of TIKOSYN therapy is 72 hours. If patients do not convert to normal sinus rhythm within 24 hours of initiation, electrical cardioversion should be re-considered. If a patient converts to normal sinus rhythm towards the end of the monitoring period, monitoring should be continued for at least 12 hours after electrical or pharmacological cardioversion.

Maintenance of TIKOSYN Therapy
The usual maintenance dose is the dose effective in converting the arrhythmia to sinus rhythm. Renal function and QTc should be re-evaluated every three months or as medically warranted. Any deterioration of renal function should result in downwards adjustment of the TIKOSYN dose (refer to the table above). If QTc exceeds 500 milliseconds (or 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.

Dose Adjustment
In patients with multiple risk factors for proarrhythmia (see Section 4.4, proarrhythmia), it may be appropriate to consider using a maximum dose of 250 micrograms twice daily, adjusted for creatinine clearance and QT interval where required. **It is critically important that if at any time the dose of TIKOSYN is increased, the patient must be rehospitalised for at least three days. Previous toleration of higher doses does not exclude the need for rehospitalisation.**

Missed doses
If a patient misses a dose, patients should be instructed NOT to double the next dose. The next dose is to be taken at the usual time. If more than one dose is missed, patients should contact their physician as soon as possible; hospitalisation for re-initiation of therapy may be required.

Use in patients with renal impairment
Dofetilide is excreted primarily via the renal route. Therefore, in patients with renal impairment, dosage should be adjusted as described above (see sections 4.2, 4.3 and 5.2).

Use in patients with hepatic impairment
No dosage adjustment is required for patients with mild or moderate hepatic impairment (Child-Pugh Class A and B). Dofetilide is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C) (see sections 4.3 and 5.2).

Use in children
The use of TIKOSYN in children under 18 years is contraindicated (see sections 4.3 and 5.3).

Use in the elderly
No additional change to dosage needs to be made for elderly patients. (see section 5.2).

Use in female patients
The recommended dose is the same for male and female patients (see section 5.2).

4.3 Contraindications

TIKOSYN is contraindicated in patients:

- with congenital or acquired long QT syndromes.
- with a known hypersensitivity to dofetilide or any of the excipients of the product.
- with baseline (pre-treatment) QTc greater than 440 msec (or 500 msec in patients with ventricular conduction abnormalities)
- with severe renal impairment (creatinine clearance <20 ml/min), including patients on dialysis
- with severe hepatic impairment
- with second or third degree AV block or sick sinus syndrome (unless a functioning pacemaker is in situ)
- with bradycardia (less than 50 bpm)
- with hypokalaemia
- under the age of 18

In addition, TIKOSYN is contraindicated in combination with the following medications: (see section 4.5):

- cimetidine
- verapamil
- ketoconazole
- QT prolonging drugs (including Class I and other Class III antiarrhythmic agents)
- drugs that inhibit the renal cation transport system (trimethoprim, megestrol and prochlorperazine)
- CYP3A4 inhibitors (e.g. azole antifungal agents, macrolide antibiotics and protease inhibitors)

4.4 Special warnings and special precautions for use

Anticoagulation:
Patients with atrial fibrillation should be anticoagulated according to standard medical practice prior to electrical or pharmacological cardioversion. Anticoagulant therapy may be continued after cardioversion according to standard medical practice.

Proarrhythmia:
Torsade de Pointes, a polymorphic form of ventricular tachycardia, is the most common manifestation of proarrhythmia with dofetilide.

In general, the following are risk factors for Torsade de Pointes: renal impairment, structural heart disease, prolonged QT interval, a low cardiac ejection fraction, bradycardia and/or abnormal plasma levels of potassium or magnesium. Hypokalemia must be corrected before initiation of TIKOSYN therapy and the dose of TIKOSYN should be adjusted according to calculated creatinine clearance and QTc as described above. The risk of proarrhythmia is greater in female patients compared to males. During the TIKOSYN clinical programme, the relative risk for Torsade de Pointes was approximately 3 fold greater in females compared to males; however, there was no increased mortality risk in females taking TIKOSYN compared to placebo.

Patients with ventricular arrhythmias:
A higher incidence of Torsade de Pointes has been observed in patients with atrial fibrillation and concomitant ventricular arrhythmias.
**Digoxin:**
The concomitant administration of digoxin with dofetilide was associated with a higher occurrence of Torsade de Pointes. Therefore, these patients should be treated with caution.

**Heart failure:**
Although dofetilide does not depress cardiac performance, the risk of proarrhythmia in patients with chronic heart failure is higher than in patients without heart failure. Experience with the use of dofetilide in severe cardiac failure (NYHA class IV) is limited. Therefore, these patients should be treated with caution and they should be carefully supervised.

If proarrhythmia occurs, TIKOSYN therapy should be discontinued. Management of Torsade de Pointes may include electrical cardioversion, temporary cardiac pacing or treatment with isoprenaline or magnesium sulphate infusion.

**Renal Impairment:**
Dosage adjustment is required based on creatinine clearance (see sections 4.2, 4.3 and 5.2).

**4.5 Interactions with other medicinal products and other forms of interaction**

**Contraindicated combinations**

**Cimetidine:** Concomitant administration of cimetidine with TIKOSYN is contraindicated. Cimetidine dosing at 400mg twice daily has been shown to increase plasma levels of dofetilide by 58%. Cimetidine doses of 100mg twice daily resulted in a 13% increase in dofetilide plasma levels. Therefore an alternative agent to cimetidine should be used (ranitidine, omeprazole, or antacids).

**Verapamil:** Concomitant use of verapamil with TIKOSYN is contraindicated. Co-administration of dofetilide with verapamil resulted in transient increases in dofetilide peak plasma levels of 43%, although overall exposure to dofetilide was not significantly increased. TIKOSYN does not affect the pharmacokinetics or pharmacodynamics of verapamil.

**Ketoconazole:** Concomitant use of ketoconazole is contraindicated. Ketoconazole at 400mg daily co-administered with dofetilide has been shown to increase dofetilide exposure by 55%.

**QT Interval Prolonging Drugs:** The co-administration of TIKOSYN with drugs known to prolong the QT interval has not been studied and is contraindicated due to the possible potentiation of the pharmacodynamic effects of dofetilide (see Section 4.3). Examples include certain neuroleptics, cisapride, bepridil, tricyclic antidepressants, certain antihistamine drugs (e.g. H1 receptor antagonists) and certain macrolide antibiotics (e.g. erythromycin).

**CYP3A4 Inhibitors:** Dofetilide is not an inhibitor of CYP3A4 nor of other cytochrome P450 isoenzymes (CYP2C9, CYP2D6). Dofetilide is metabolised by the CYP3A4 isoenzyme of the P450 cytochrome system. However, it has a low affinity for this isoenzyme. Inhibitors of this isoenzyme could potentially increase systemic dofetilide exposure. Therefore these drugs are contraindicated in combination with TIKOSYN (see section 4.3). CYP3A4 inhibitors include: macrolide antibiotics (e.g. erythromycin),azole antifungal agents (e.g. ketoconazole) and protease inhibitors (e.g. ritonavir).

**Clinically significant interactions**
Inhibitors of renal cation secretion: Dofetilide is eliminated by renal cation secretion. The magnitude of the effect that cimetidine and ketoconazole have on the renal clearance of dofetilide suggests that these drugs are contraindicated in combination with TIKOSYN.

Renal cation transport inhibitors include: trimethoprim, prochlorperazine and megestrol. Azole antifungal agents (e.g. itraconazole) may also inhibit renal transport of dofetilide. In addition, caution should be taken when drugs that are actively secreted via this route are co-administered with dofetilide e.g. triamterene, metformin and amiloride.

Use with Class I and Class III antiarrhythmic agents: The use of dofetilide in conjunction with other antiarrhythmic drugs that prolong the QT interval has not been studied but is contraindicated due to the possible potentiation of the pharmacodynamic effects of dofetilide (see section 4.3). Class I or class III agents should be withheld for at least three half-lives prior to dosing with dofetilide. In clinical trials, TIKOSYN was only administered to patients previously treated with amiodarone if amiodarone levels were below 0.3 μg/ml or after amiodarone had been withdrawn for three months (see section 4.2).

Potassium-depleting diuretics: Hypokalaemia or hypomagnesaemia may occur with administration of potassium-depleting diuretics, increasing the potential for Torsade de Pointes. Potassium levels should be within the normal range prior to administration of TIKOSYN and maintained in the normal range during administration of TIKOSYN.
Other drug interaction information

Studies in healthy volunteers have shown that dofetilide does not affect the pharmacokinetics or pharmacodynamics of concomitant medications such as: warfarin, digoxin, propranolol, phenytoin, theophylline and oral contraceptives.

In healthy volunteers, amlodipine, phenytoin, glibenclamide, ranitidine, omeprazole, hormone replacement therapy (a combination of conjugated oestrogens and medroxyprogesterone), antacid (aluminium and magnesium hydroxide) and theophylline did not affect the pharmacokinetics of dofetilide.

In a population pharmacokinetic analysis of 1445 patients, drugs in the following groups were shown to have no clinically significant interaction with dofetilide: ACE inhibitors, oral anticoagulants, calcium channel blockers, beta blockers, cardiac glycosides, inducers of cytochrome P450 3A4, substrates and inhibitors of cytochrome P450 3A4, substrates and inhibitors of P-glycoprotein, sulphonylureas, nitrates, loop diuretics, potassium sparing diuretics, substrates of tubular cation transport, and QT prolonging drugs. Differences in clearance between patients on these medications and those off these medications varied between -16% and +3%. The mean clearances of dofetilide was 16% and 15% lower in patients taking thiazide diuretics and inhibitors of tubular organic cation transport, respectively. However see section 4.3 Contraindications.

**Food:** The bioavailability of dofetilide is not affected by the concomitant ingestion of food although the time to maximum plasma concentration is prolonged to 3-4 hours.

4.6 Pregnancy and lactation

For TIKOSYN no clinical data on exposed pregnancies are available. Studies in animals have shown reproductive toxicity (see section 5.3). The relevance of these data for humans is unknown; therefore TIKOSYN should not be used during pregnancy unless clearly necessary.

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

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic profile and clinical experience, there is no evidence to suggest that dofetilide affects the ability to drive or use machines.

4.8 Undesirable effects

Dofetilide has been administered to more than 5000 subjects in clinical trials.

The most serious dose related undesirable effect with TIKOSYN is Torsade de Pointes. This is the most common manifestation of proarrhythmia that is observed in association with QT-prolonging drugs including dofetilide. The overall incidence of Torsade de Pointes observed in patients with supraventricular arrhythmia was 0.8% (11/1346). In the DIAMOND CHF population (see section 5.1) the incidence of Torsade de Pointes was 3.3% (25/762) and in DIAMOND MI it was 0.9% (7/749). The majority of Torsade de Pointes episodes occurred within the first three days of TIKOSYN therapy.

In addition, the following undesirable effects have been observed in patients being treated for supraventricular arrhythmias at the recommended clinical dose. The placebo-corrected incidence is shown in brackets.
Body as a whole: asthenia (0.4%), headache (1.1%)
Digestive: nausea (0.6%)
Nervous system: dizziness (0.5%)
Respiratory: dyspnoea (0.5%)

Increases in eosinophil and monocyte counts and low plasma magnesium levels have been reported in patients receiving dofetilide. Mild elevations of serum transaminases have been seen in clinical studies, although at the recommended dose of dofetilide the incidence was similar to placebo-treated patients. Rare cases of thrombocytopenia have been observed in clinical studies although a causal relationship to dofetilide has not been established.

4.9 Overdose

The most prominent manifestation of overdosage is likely to be excessive prolongation of the QTc interval and the occurrence of Torsade de Pointes.

In cases of overdose when QTc interval exceeds 500 msec (or 550 msec in patients with ventricular conduction abnormalities) cardiac monitoring should be initiated in hospital. Close medical monitoring and supervision should continue until the QTc interval returns to baseline levels. There is no known antidote to dofetilide, therefore treatment of overdose should be symptomatic and supportive. Charcoal slurry may be given soon after overdosing but has only been seen to be useful when given within 15 minutes of dofetilide administration (T<sub>max</sub> is 2-3 hours).

Experience has shown that administration of isoprenaline infusion, with or without cardiac pacing is effective in treating prolongation of the QTc interval. Administration of intravenous magnesium sulphate may also be effective in the management of Torsade de Pointes. In vitro studies have shown that dofetilide is only slowly removed by dialysis; therefore this treatment is unlikely to be useful in the management of acute overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiarrhythmics
ATC code: C01BD04

Mechanism of action:
Dofetilide is a highly selective Class III antiarrhythmic agent (according to the Vaughan Williams classification) and blocks a single cardiac potassium channel (I<sub>Kr</sub>). At clinically relevant concentrations dofetilide does not have any effect on sodium channels (associated with Class I effects), calcium channels (associated with Class IV effects) or other potassium channels and has no beta blocking (Class II) or alpha-adrenergic blocking activity.

Electrophysiology and haemodynamics:
Dofetilide has no negative inotropic effects in patients with normal or with severely impaired left ventricular function. Dofetilide causes a reduction in heart rate (4-8 beats per minute) and has no effect on conduction velocity, blood pressure, PR interval or QRS width.

Dofetilide selectively prolongs the QT interval of the ECG, the monophasic action potential duration and the effective refractory period in a concentration dependent manner in volunteers. In animal models the atria have been shown to be more sensitive to the effects of dofetilide than the ventricles.
Pharmacokinetic - pharmacodynamic relationship:
In healthy volunteers and in patients with supraventricular or ventricular tachyarrhythmias, ischaemic heart disease or renal impairment, the relationship between dofetilide plasma levels and prolongation of QTc was linear. The maximum prolongation of QTc was usually observed during days 2-3 of therapy.

Further information on clinical studies:
Dofetilide has been administered to a total of more than 3400 patients for a mean duration of over 9 months for the treatment of supraventricular and ventricular arrhythmias.

Dofetilide was significantly superior to placebo in converting patients from atrial fibrillation and/or atrial flutter to normal sinus rhythm. In two clinical studies, conversion rates were 30% for patients receiving dofetilide compared to 1% for placebo. As with other therapies, factors associated with improved likelihood of conversion to normal sinus rhythm include patients presenting with atrial flutter (as opposed to atrial fibrillation) and normal to moderately enlarged left atrial diameter (as opposed to severely enlarged left atrium). In clinical studies, the conversion rate was 56% for atrial flutter and 26% for atrial fibrillation.

In the two pivotal studies in patients with atrial fibrillation/atrial flutter, dofetilide was associated with a statistically significant increase in the number of patients maintained in normal sinus rhythm following electrical cardioversion or conversion with dofetilide when compared to placebo-treated patients. At the recommended dose, the probability of remaining in sinus rhythm in the two studies after 6 months was 62% and 71% whereas the equivalent probability for placebo-treated patients was 37% and 26% respectively.

In patients with supraventricular arrhythmias, dofetilide converts and maintains sinus rhythm which is associated with a reduction in frequency and severity of arrhythmia-induced symptoms (shortness of breath and palpitations), an increased exercise tolerance and an improvement in quality of life. In a pooled analysis of patients with supraventricular arrhythmias, survival rates in patients treated with dofetilide and placebo were comparable.

DIAMOND survival studies: Dofetilide was administered to 1511 patients for up to 3 years in the DIAMOND (Danish Investigations of Arrhythmia and Mortality on Dofetilide) studies. These studies recruited patients with compromised left ventricular function (ejection fraction ≤ 35%) in addition to having either symptomatic heart failure (DIAMOND CHF) or a recent myocardial infarction (DIAMOND MI) within the previous 7 days. Patients in the DIAMOND CHF study, when treated with dofetilide, had a one year survival of 73% compared to 72% in placebo-treated patients. In addition, dofetilide reduced the incidence of hospitalisations in patients with worsening congestive heart failure with one year event-free survival of 71% on dofetilide and 60% on placebo. DIAMOND MI showed that for patients with recent myocardial infarction, survival after 1 year was 79% for patients taking dofetilide compared to 77% on placebo. These data show that dofetilide was not associated with an increased risk of mortality in patients with CHF or following recent MI.

Other studies: Dofetilide reduces the defibrillation threshold in patients undergoing implantation of a cardioverter defibrillator device (ICD) and can be used safely in patients with ICDs.

5.2 Pharmacokinetic properties

Absorption: In healthy subjects, the oral bioavailability of dofetilide is >90%. Maximum observed plasma concentrations occur at about 2-3 hours in the fasted state.
Bioavailability is unaffected by food or antacid. Steady state plasma concentrations are attained within 2-3 days and can be predicted from a single dose. Over the clinical dose range, plasma concentrations increase in a predictable, linear fashion with dose. Variability in plasma concentrations within and between subjects is low.

**Distribution:** Plasma protein binding of dofetilide is 60-70% and is independent of plasma concentration. Plasma protein binding of dofetilide is unaffected by renal impairment. Mean volume of distribution is approximately 3 L/kg and is linearly correlated with body weight.

**Metabolism:** Metabolism is a minor component of dofetilide elimination. *In vitro* studies with human liver microsomes show that dofetilide is predominantly metabolised by the cytochrome P450 isoenzyme, CYP3A4; however it has a low affinity for this isoenzyme. Metabolites are formed by N-dealkylation and N-oxidation. There are no quantifiable metabolites circulating in plasma.

**Elimination:** The terminal half-life is approximately 10 hours. Approximately 80% of a single dose of dofetilide is excreted in urine. Seventy percent of dofetilide is excreted unchanged in urine with the remainder converted to metabolites. Renal elimination involves both glomerular filtration and active cation secretion (which can be inhibited by cimetidine and ketoconazole).
Pharmacokinetics in special groups

Renal impairment: In volunteers with varying degrees of renal impairment and patients with arrhythmias there is a linear relationship between clearance of dofetilide and creatinine clearance. In clinical studies the half-life of dofetilide in subjects with low creatinine clearance was also extended. Thus, dosage adjustment is required based on creatinine clearance (see section 4.2).

Hepatic impairment: There was no clinically significant alteration in the pharmacokinetics of dofetilide in volunteers with mild to moderate hepatic impairment (Child-Pugh Class A and B) compared to age and weight matched healthy volunteers. Patients with severe hepatic impairment (Child-Pugh Class C) were not studied. (see section 4.2)

Patients with arrhythmias: Population pharmacokinetic analyses of dofetilide given orally indicate that the plasma concentrations are similar between patients treated for supraventricular arrhythmias or ventricular tachycardia and normal healthy volunteers, after adjustment has been made for renal function.

Patients with heart disease: Studies with intravenously administered dofetilide showed that there was no difference in pharmacokinetic parameters between patients with ischaemic heart disease and healthy volunteers. In addition, dofetilide pharmacokinetics were independent of NYHA classification of heart failure, left ventricular ejection fraction or underlying heart disease (e.g. angina, congestive heart failure, myocardial infarction).

Elderly: Apparent clearance was significantly lower and plasma concentrations 25% higher in elderly (>65 years) compared to young healthy volunteers. However, this reduced clearance is accounted for primarily by a reduction in renal function which occurs in the elderly and any dosage adjustment should be made on the basis of creatinine clearance (see section 4.2).

Female patients: Female patients have approximately 12-18% lower dofetilide clearances (approximately 14-22% higher dofetilide levels) compared to men. In females, as in males, renal function was the single greatest factor influencing dofetilide clearance. (see section 4.2).

5.3 Preclinical safety

Testicular atrophy: Repeat dose studies of 24 months duration in mice and 12 months duration in rats and dogs indicate that dofetilide is associated with testicular atrophy in these species. The testicular atrophy was observed only at exposures considered to be sufficiently in excess of the maximum human systemic exposure, indicating little relevance to clinical use. The effects are considered to be a direct pharmacological action since no changes have been observed in hormones related to testicular function in rats or man.

Reproductive toxicology: Dofetilide has been shown to be embryotoxic and teratogenic in rats and embryotoxic in mice. In these animals, the systemic exposure at which these effects were seen are respectively 6- and 2-fold greater than the maximum recommended clinical exposure. Dofetilide does not impair fertility when administered to male or female rats using an oral dose of 1mg/kg/day or an intravenous dose of 4 mg/kg/day. The intravenous dose used in these studies corresponds to systemic exposure multiples of 34 compared to the maximum recommended clinical dose. The dose used in oral fertility studies was chosen in order to avoid embryolethality in pregnant females.
Carcinogenicity and genotoxicity:
Dofetilide does not cause carcinogenic effects when administered to mice or rats and shows no evidence of genotoxicity.
6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsules:
Microcrystalline cellulose
Maize starch
Colloidal anhydrous silica
Magnesium stearate

Capsule Shell:
Gelatin
Titanium dioxide (E171)
FD&C Yellow 6 (E110)
Black ink containing black iron oxide (E172), shellac, soya lecithin and anti-foam DC 1510

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and content of container

High density polyethylene bottles containing 200 capsules with child-resistant, lined polypropylene caps or lined metal caps.

Aclar blisters containing 14, 28, 56 or 100 capsules per carton.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ, UK

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT
1. **NAME OF THE MEDICINAL PRODUCT**

TIKOSYN 250 microgram hard capsules

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each capsule contains 250 micrograms of dofetilide

3. **PHARMACEUTICAL FORM**

Capsules, hard

TIKOSYN 250 microgram capsules are peach and are marked with TKN 250 PFIZER

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Tikosyn is a Class III antiarrhythmic agent that is indicated for the following:

(i) Conversion of persistent atrial fibrillation or atrial flutter to normal sinus rhythm in patients in whom cardioversion by electrical means is not appropriate and in whom the duration of the arrhythmic episode is less than 6 months (see section 5.1).

(ii) Maintenance of sinus rhythm (after conversion) in patients with persistent atrial fibrillation or atrial flutter. Because TIKOSYN can cause ventricular arrhythmias, it should be reserved for patients in whom atrial fibrillation/atrial flutter is highly symptomatic and in whom other antiarrhythmic therapy is not appropriate.

Dofetilide has not been shown to be effective in patients with paroxysmal atrial arrhythmias (including paroxysmal atrial fibrillation).

4.2 **Posology and Method of Administration**

- During treatment with TIKOSYN, patients must be managed by a specialist experienced in the treatment of arrhythmias.
- Therapy with TIKOSYN must be initiated in an in-patient setting that provides continuous ECG monitoring. Patients should be monitored for at least the first three days (72 hours) of TIKOSYN therapy and for at least 12 hours after electrical or pharmacological conversion.
- TIKOSYN capsules can be taken with or without food.
- The dose of TIKOSYN must be individualised for every patient according to calculated creatinine clearance, cardiac status (see below) and QTc.

**Measurement of QT Interval:**

Prior to administration of the first dose, the QTc must be determined using an average of 5-10 beats. For patients with a heart rate greater than 60 beats per minute, QTc is calculated using Bazett’s formula as follows: QTc = QT / √RR. However, if the heart rate is less than 60 bpm, QT (not QTc) interval should be used. If the QTc (or QT interval as appropriate) is greater
than 440 msec (or 500 msec in patients with ventricular conduction abnormalities), TIKOSYN is contraindicated.

**Calculation of Creatinine Clearance**

Prior to the administration of the first dose the patient’s creatinine clearance must be calculated. This is calculated from serum creatinine (μmol/l) using the following formula:

\[
\text{creatinine clearance (male)} = \frac{(140-\text{age}) \times \text{body weight in kg} \times 1.22}{\text{serum creatinine (μmol/l)}} \text{ ml/min}
\]

\[
\text{creatinine clearance (female)} = \frac{(140-\text{age}) \times \text{body weight in kg} \times 1.04}{\text{serum creatinine (μmol/l)}} \text{ ml/min}
\]

When serum creatinine is in mg/dl, the calculated value obtained must be multiplied by 88.4 (1 mg/dl = 88.4 μmol/l) to determine the creatinine clearance.

**Dose regimen**

- The maximum recommended dose is 500 micrograms twice daily for patients with normal renal function and normal cardiac status. Patients with symptomatic heart failure or recent myocardial infarction (MI), with left ventricular dysfunction (ejection fraction (EF) ≤ 35%) should not receive doses in excess of 250 micrograms twice daily.
- TIKOSYN must only be dosed according to the flow chart, taking into account the patient’s baseline QTc, creatinine clearance and cardiac status (see below).

**Starting dose for conversion and maintenance**

TIKOSYN is contraindicated when the baseline QTc interval is >440 msec.

In patients with baseline QTc ≤ 440 msec, the starting dose of TIKOSYN is summarised below and is detailed in the following flow chart:

<table>
<thead>
<tr>
<th>Calculated creatinine clearance:</th>
<th>Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with symptomatic CHF or recent MI with ejection fraction ≤ 35%</td>
<td>Other patients</td>
</tr>
<tr>
<td>&gt; 60 ml/min</td>
<td>250 micrograms twice daily</td>
</tr>
<tr>
<td>&gt;40≤60 ml/min</td>
<td>250 micrograms twice daily</td>
</tr>
<tr>
<td>≥20≤40 ml/min</td>
<td>125 micrograms twice daily</td>
</tr>
<tr>
<td>&lt; 20 ml/min</td>
<td>Dofetilide is contraindicated in these patients.</td>
</tr>
</tbody>
</table>
Place Patient on continuous ECG monitoring

Check baseline QTc
If QTc > 440 msec, do not use TIKOSYN
If QTc ≤ 440 msec, proceed

Calculate creatinine clearance (CLcr)

If CLcr < 20 ml/min, dofetilide is CONTRAINDIATED

If CLcr is > 60 ml/min, assess cardiac status
If patients have symptomatic CHF or recent MI, with EF ≤ 35%, start with 250 micrograms twice daily
For other patients start with 500 micrograms twice daily

If CLcr is = 40-60 ml/min, start with 250 micrograms dofetilide twice daily

If CLcr is = 20-<40 ml/min, start with 125 micrograms dofetilide twice daily

2-3 hours after the first dose check the QTc

(Post first dose only)
If increase in QTc is ≤ 15%, continue current dose

(Post first dose only)
If increase in QTc is > 15% or QTc is > 500 msec,
Decrease The Dose:
if 500 micrograms BID, reduce to 250 micrograms BID
if 250 micrograms BID, reduce to 125 micrograms BID
if 125 micrograms BID, reduce to 125 micrograms OD

QTc must be determined 2-3 hours after each in-patient dose.
If at any time after the second dose QTc increases above 500 msec dofetilide should be discontinued
Special Considerations

Switch to TIKOSYN capsules from Class I or other Class III antiarrhythmic therapy
Before initiating TIKOSYN capsules, previous Class I or Class III antiarrhythmic therapy should be withdrawn for a minimum of 3 plasma half-lives. Due to the unpredictable pharmacokinetics of amiodarone, TIKOSYN capsules should not be initiated following amiodarone therapy until amiodarone plasma levels are below 0.3 μg/ml or after amiodarone has been withdrawn for three months.

Cardioversion
The minimum monitoring period after initiation of TIKOSYN therapy is 72 hours. If patients do not convert to normal sinus rhythm within 24 hours of initiation, electrical cardioversion should be re-considered. If a patient converts to normal sinus rhythm towards the end of the monitoring period, monitoring should be continued for at least 12 hours after electrical or pharmacological cardioversion.

Maintenance of TIKOSYN Therapy
The usual maintenance dose is the dose effective in converting the arrhythmia to sinus rhythm. Renal function and QTc should be re-evaluated every three months or as medically warranted. Any deterioration of renal function should result in downwards adjustment of the TIKOSYN dose (refer to the table above). If QTc exceeds 500 milliseconds (or 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.

Dose Adjustment
In patients with multiple risk factors for proarrhythmia (see Section 4.4, proarrhythmia), it may be appropriate to consider using a maximum dose of 250 micrograms twice daily, adjusted for creatinine clearance and QT interval where required. It is critically important that if at any time the dose of TIKOSYN is increased, the patient must be rehospitalised for at least three days. Previous toleration of higher doses does not exclude the need for rehospitalisation.

Missed doses
If a patient misses a dose, patients should be instructed NOT to double the next dose. The next dose is to be taken at the usual time. If more than one dose is missed, patients should contact their physician as soon as possible; hospitalisation for re-initiation of therapy may be required.

Use in patients with renal impairment
Dofetilide is excreted primarily via the renal route. Therefore, in patients with renal impairment, dosage should be adjusted as described above (see sections 4.2, 4.3 and 5.2).

Use in patients with hepatic impairment
No dosage adjustment is required for patients with mild or moderate hepatic impairment (Child-Pugh Class A and B). Dofetilide is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C) (see sections 4.3 and 5.2).

Use in children
The use of TIKOSYN in children under 18 years is contraindicated (see sections 4.3 and 5.3).

Use in the elderly
No additional change to dosage needs to be made for elderly patients. (see section 5.2).

Use in female patients
The recommended dose is the same for male and female patients (see section 5.2).

4.3 Contraindications

TIKOSYN is contraindicated in patients:

- with congenital or acquired long QT syndromes.
- with a known hypersensitivity to dofetilide or any of the excipients of the product.
- with baseline (pre-treatment) QTc greater than 440 msec (or 500 msec in patients with ventricular conduction abnormalities)
- with severe renal impairment (creatinine clearance <20 ml/min), including patients on dialysis
- with severe hepatic impairment
- with second or third degree AV block or sick sinus syndrome (unless a functioning pacemaker is in situ)
- with bradycardia (less than 50 bpm)
- with hypokalaemia
- under the age of 18

In addition, TIKOSYN is contraindicated in combination with the following medications: (see section 4.5):
- cimetidine
- verapamil
- ketoconazole
- QT prolonging drugs (including Class I and other Class III antiarrhythmic agents)
- drugs that inhibit the renal cation transport system (trimethoprim, megestrol and prochlorperazine)
- CYP3A4 inhibitors (e.g. azole antifungal agents, macrolide antibiotics and protease inhibitors)

4.4 Special warnings and special precautions for use

Anticoagulation:
Patients with atrial fibrillation should be anticoagulated according to standard medical practice prior to electrical or pharmacological cardioversion. Anticoagulant therapy may be continued after cardioversion according to standard medical practice.

Proarrhythmia:
Torsade de Pointes, a polymorphic form of ventricular tachycardia, is the most common manifestation of proarrhythmia with dofetilide.

In general, the following are risk factors for Torsade de Pointes: renal impairment, structural heart disease, prolonged QT interval, a low cardiac ejection fraction, bradycardia and/or abnormal plasma levels of potassium or magnesium. Hypokalemia must be corrected before initiation of TIKOSYN therapy and the dose of TIKOSYN should be adjusted according to calculated creatinine clearance and QTc as described above. The risk of proarrhythmia is greater in female patients compared to males. During the TIKOSYN clinical programme, the relative risk for Torsade de Pointes was approximately 3 fold greater in females compared to males; however, there was no increased mortality risk in females taking TIKOSYN compared to placebo.

Patients with ventricular arrhythmias:
A higher incidence of Torsade de Pointes has been observed in patients with atrial fibrillation and concomitant ventricular arrhythmias.
**Digoxin:**  
The concomitant administration of digoxin with dofetilide was associated with a higher occurrence of Torsade de Pointes. Therefore, these patients should be treated with caution.

**Heart failure:**  
Although dofetilide does not depress cardiac performance, the risk of proarrhythmia in patients with chronic heart failure is higher than in patients without heart failure. Experience with the use of dofetilide in severe cardiac failure (NYHA class IV) is limited. Therefore, these patients should be treated with caution and they should be carefully supervised.

If proarrhythmia occurs, TIKOSYN therapy should be discontinued. Management of Torsade de Pointes may include electrical cardioversion, temporary cardiac pacing or treatment with isoprenaline or magnesium sulphate infusion.

**Renal Impairment:**  
Dosage adjustment is required based on creatinine clearance (see sections 4.2, 4.3 and 5.2).

### 4.5 Interactions with other medicinal products and other forms of interaction

#### Contraindicated combinations

**Cimetidine:** Concomitant administration of cimetidine with TIKOSYN is contraindicated. Cimetidine dosing at 400mg twice daily has been shown to increase plasma levels of dofetilide by 58%. Cimetidine doses of 100mg twice daily resulted in a 13% increase in dofetilide plasma levels. Therefore an alternative agent to cimetidine should be used (ranitidine, omeprazole, or antacids).

**Verapamil:** Concomitant use of verapamil with TIKOSYN is contraindicated. Co-administration of dofetilide with verapamil resulted in transient increases in dofetilide peak plasma levels of 43%, although overall exposure to dofetilide was not significantly increased. TIKOSYN does not affect the pharmacokinetics or pharmacodynamics of verapamil.

**Ketoconazole:** Concomitant use of ketoconazole is contraindicated. Ketoconazole at 400mg daily co-administered with dofetilide has been shown to increase dofetilide exposure by 55%.

**QT Interval Prolonging Drugs:** The co-administration of TIKOSYN with drugs known to prolong the QT interval has not been studied and is contraindicated due to the possible potentiation of the pharmacodynamic effects of dofetilide (see Section 4.3). Examples include certain neuroleptics, cisapride, bepridil, tricyclic antidepressants, certain antihistamine drugs (e.g. H₁ receptor antagonists) and certain macrolide antibiotics (e.g. erythromycin).

**CYP3A4 Inhibitors:** Dofetilide is not an inhibitor of CYP3A4 nor of other cytochrome P450 isoenzymes (CYP2C9, CYP2D6). Dofetilide is metabolised by the CYP3A4 isoenzyme of the P450 cytochrome system. However, it has a low affinity for this isoenzyme. Inhibitors of this isoenzyme could potentially increase systemic dofetilide exposure. Therefore these drugs are contraindicated in combination with TIKOSYN (see section 4.3). CYP3A4 inhibitors include: macrolide antibiotics (e.g. erythromycin), azole antifungal agents (e.g. ketoconazole) and protease inhibitors (e.g. ritonavir).

**Clinically significant interactions**
Inhibitors of renal cation secretion: Dofetilide is eliminated by renal cation secretion. The magnitude of the effect that cimetidine and ketoconazole have on the renal clearance of dofetilide suggests that these drugs are contraindicated in combination with TIKOSYN.

Renal cation transport inhibitors include: trimethoprim, prochlorperazine and megestrol. Azole antifungal agents (e.g. itraconazole) may also inhibit renal transport of dofetilide. In addition, caution should be taken when drugs that are actively secreted via this route are co-administered with dofetilide e.g. triamterene, metformin and amiloride.

Use with Class I and Class III antiarrhythmic agents: The use of dofetilide in conjunction with other antiarrhythmic drugs that prolong the QT interval has not been studied but is contraindicated due to the possible potentiation of the pharmacodynamic effects of dofetilide (see section 4.3). Class I or class III agents should be withheld for at least three half-lives prior to dosing with dofetilide. In clinical trials, TIKOSYN was only administered to patients previously treated with amiodarone if amiodarone levels were below 0.3 μg/ml or after amiodarone had been withdrawn for three months (see section 4.2).

Potassium-depleting diuretics: Hypokalaemia or hypomagnesaemia may occur with administration of potassium-depleting diuretics, increasing the potential for Torsade de Pointes. Potassium levels should be within the normal range prior to administration of TIKOSYN and maintained in the normal range during administration of TIKOSYN.
Other drug interaction information

Studies in healthy volunteers have shown that dofetilide does not affect the pharmacokinetics or pharmacodynamics of concomitant medications such as: warfarin, digoxin, propranolol, phenytoin, theophylline and oral contraceptives.

In healthy volunteers, amlodipine, phenytoin, glibenclamide, ranitidine, omeprazole, hormone replacement therapy (a combination of conjugated oestrogens and medroxyprogesterone), antacid (aluminium and magnesium hydroxide) and theophylline did not affect the pharmacokinetics of dofetilide.

In a population pharmacokinetic analysis of 1445 patients, drugs in the following groups were shown to have no clinically significant interaction with dofetilide: ACE inhibitors, oral anticoagulants, calcium channel blockers, beta blockers, cardiac glycosides, inducers of cytochrome P450 3A4, substrates and inhibitors of cytochrome P450 3A4, substrates and inhibitors of P-glycoprotein, sulphonylureas, nitrates, loop diuretics, potassium sparing diuretics, substrates of tubular cation transport, and QT prolonging drugs. Differences in clearance between patients on these medications and those off these medications varied between -16% and +3%. The mean clearances of dofetilide was 16% and 15% lower in patients taking thiazide diuretics and inhibitors of tubular organic cation transport, respectively. However see section 4.3 Contraindications.

Food: The bioavailability of dofetilide is not affected by the concomitant ingestion of food although the time to maximum plasma concentration is prolonged to 3-4 hours.

4.6 Pregnancy and lactation

For TIKOSYN no clinical data on exposed pregnancies are available. Studies in animals have shown reproductive toxicity (see section 5.3). The relevance of these data for humans is unknown; therefore TIKOSYN should not be used during pregnancy unless clearly necessary.

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

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic profile and clinical experience, there is no evidence to suggest that dofetilide affects the ability to drive or use machines.

4.8 Undesirable effects

Dofetilide has been administered to more than 5000 subjects in clinical trials.

The most serious dose related undesirable effect with TIKOSYN is Torsade de Pointes. This is the most common manifestation of proarhythmia that is observed in association with QT-prolonging drugs including dofetilide. The overall incidence of Torsade de Pointes observed in patients with supraventricular arrhythmia was 0.8% (11/1346). In the DIAMOND CHF population (see section 5.1) the incidence of Torsade de Pointes was 3.3% (25/762) and in DIAMOND MI it was 0.9% (7/749). The majority of Torsade de Pointes episodes occurred within the first three days of TIKOSYN therapy.

In addition, the following undesirable effects have been observed in patients being treated for supraventricular arrhythmias at the recommended clinical dose. The placebo-corrected incidence is shown in brackets.
Body as a whole: asthenia (0.4%), headache (1.1%)  
Digestive: nausea (0.6%)  
Nervous system: dizziness (0.5%)  
Respiratory: dyspnœa (0.5%)  

Increases in eosinophil and monocyte counts and low plasma magnesium levels have been reported in patients receiving dofetilide. Mild elevations of serum transaminases have been seen in clinical studies, although at the recommended dose of dofetilide the incidence was similar to placebo-treated patients. Rare cases of thrombocytopenia have been observed in clinical studies although a causal relationship to dofetilide has not been established.

4.9 Overdose

The most prominent manifestation of overdosage is likely to be excessive prolongation of the QTc interval and the occurrence of Torsade de Pointes. In cases of overdose when QTc interval exceeds 500 msec (or 550 msec in patients with ventricular conduction abnormalities) cardiac monitoring should be initiated in hospital. Close medical monitoring and supervision should continue until the QTc interval returns to baseline levels. There is no known antidote to dofetilide, therefore treatment of overdose should be symptomatic and supportive. Charcoal slurry may be given soon after overdosing but has only been seen to be useful when given within 15 minutes of dofetilide administration ($T_{\text{max}}$ is 2-3 hours). Experience has shown that administration of isoprenaline infusion, with or without cardiac pacing is effective in treating prolongation of the QTc interval. Administration of intravenous magnesium sulphate may also be effective in the management of Torsade de Pointes.  

In vitro studies have shown that dofetilide is only slowly removed by dialysis; therefore this treatment is unlikely to be useful in the management of acute overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiarrhythmics  
ATC code: C01BD04

Mechanism of action:
Dofetilide is a highly selective Class III antiarrhythmic agent (according to the Vaughan Williams classification) and blocks a single cardiac potassium channel ($I_{\text{Kr}}$). At clinically relevant concentrations dofetilide does not have any effect on sodium channels (associated with Class I effects), calcium channels (associated with Class IV effects) or other potassium channels and has no beta blocking (Class II) or alpha-adrenergic blocking activity.

Electrophysiology and haemodynamics:
Dofetilide has no negative inotropic effects in patients with normal or with severely impaired left ventricular function. Dofetilide causes a reduction in heart rate (4-8 beats per minute) and has no effect on conduction velocity, blood pressure, PR interval or QRS width.

Dofetilide selectively prolongs the QT interval of the ECG, the monophasic action potential duration and the effective refractory period in a concentration dependent manner in volunteers. In animal models the atria have been shown to be more sensitive to the effects of dofetilide than the ventricles.
**Pharmacokinetic - pharmacodynamic relationship:**
In healthy volunteers and in patients with supraventricular or ventricular tachyarrhythmias, ischaemic heart disease or renal impairment, the relationship between dofetilide plasma levels and prolongation of QTc was linear. The maximum prolongation of QTc was usually observed during days 2-3 of therapy.

**Further information on clinical studies:**
Dofetilide has been administered to a total of more than 3400 patients for a mean duration of over 9 months for the treatment of supraventricular and ventricular arrhythmias.

Dofetilide was significantly superior to placebo in converting patients from atrial fibrillation and/or atrial flutter to normal sinus rhythm. In two clinical studies, conversion rates were 30% for patients receiving dofetilide compared to 1% for placebo. As with other therapies, factors associated with improved likelihood of conversion to normal sinus rhythm include patients presenting with atrial flutter (as opposed to atrial fibrillation) and normal to moderately enlarged left atrial diameter (as opposed to severely enlarged left atrium). In clinical studies, the conversion rate was 56% for atrial flutter and 26% for atrial fibrillation.

In the two pivotal studies in patients with atrial fibrillation/atrial flutter, dofetilide was associated with a statistically significant increase in the number of patients maintained in normal sinus rhythm following electrical cardioversion or conversion with dofetilide when compared to placebo-treated patients. At the recommended dose, the probability of remaining in sinus rhythm in the two studies after 6 months was 62% and 71% whereas the equivalent probability for placebo-treated patients was 37% and 26% respectively.

In patients with supraventricular arrhythmias, dofetilide converts and maintains sinus rhythm which is associated with a reduction in frequency and severity of arrhythmia-induced symptoms (shortness of breath and palpitations), an increased exercise tolerance and an improvement in quality of life. In a pooled analysis of patients with supraventricular arrhythmias, survival rates in patients treated with dofetilide and placebo were comparable.

DIAMOND survival studies: Dofetilide was administered to 1511 patients for up to 3 years in the DIAMOND (Danish Investigations of Arrhythmia and Mortality on Dofetilide) studies. These studies recruited patients with compromised left ventricular function (ejection fraction $\leq 35\%$) in addition to having either symptomatic heart failure (DIAMOND CHF) or a recent myocardial infarction (DIAMOND MI) within the previous 7 days. Patients in the DIAMOND CHF study, when treated with dofetilide, had a one year survival of 73% compared to 72% in placebo-treated patients. In addition, dofetilide reduced the incidence of hospitalisations in patients with worsening congestive heart failure with one year event-free survival of 71% on dofetilide and 60% on placebo. DIAMOND MI showed that for patients with recent myocardial infarction, survival after 1 year was 79% for patients taking dofetilide compared to 77% on placebo. These data show that dofetilide was not associated with an increased risk of mortality in patients with CHF or following recent MI.

**Other studies:** Dofetilide reduces the defibrillation threshold in patients undergoing implantation of a cardioverter defibrillator device (ICD) and can be used safely in patients with ICDs.

**5.2 Pharmacokinetic properties**

**Absorption:** In healthy subjects, the oral bioavailability of dofetilide is >90%. Maximum observed plasma concentrations occur at about 2-3 hours in the fasted state.
Bioavailability is unaffected by food or antacid. Steady state plasma concentrations are attained within 2-3 days and can be predicted from a single dose. Over the clinical dose range, plasma concentrations increase in a predictable, linear fashion with dose. Variability in plasma concentrations within and between subjects is low.

**Distribution:** Plasma protein binding of dofetilide is 60-70% and is independent of plasma concentration. Plasma protein binding of dofetilide is unaffected by renal impairment. Mean volume of distribution is approximately 3 L/kg and is linearly correlated with body weight.

**Metabolism:** Metabolism is a minor component of dofetilide elimination. *In vitro* studies with human liver microsomes show that dofetilide is predominantly metabolised by the cytochrome P450 isoenzyme, CYP3A4; however it has a low affinity for this isoenzyme. Metabolites are formed by N-dealkylation and N-oxidation. There are no quantifiable metabolites circulating in plasma.

**Elimination:** The terminal half-life is approximately 10 hours. Approximately 80% of a single dose of dofetilide is excreted in urine. Seventy percent of dofetilide is excreted unchanged in urine with the remainder converted to metabolites. Renal elimination involves both glomerular filtration and active cation secretion (which can be inhibited by cimetidine and ketoconazole).
Pharmacokinetics in special groups

Renal impairment: In volunteers with varying degrees of renal impairment and patients with arrhythmias there is a linear relationship between clearance of dofetilide and creatinine clearance. In clinical studies the half-life of dofetilide in subjects with low creatinine clearance was also extended. Thus, dosage adjustment is required based on creatinine clearance (see section 4.2).

Hepatic impairment: There was no clinically significant alteration in the pharmacokinetics of dofetilide in volunteers with mild to moderate hepatic impairment (Child-Pugh Class A and B) compared to age and weight matched healthy volunteers. Patients with severe hepatic impairment (Child-Pugh Class C) were not studied. (see section 4.2)

Patients with arrhythmias: Population pharmacokinetic analyses of dofetilide given orally indicate that the plasma concentrations are similar between patients treated for supraventricular arrhythmias or ventricular tachycardia and normal healthy volunteers, after adjustment has been made for renal function.

Patients with heart disease: Studies with intravenously administered dofetilide showed that there was no difference in pharmacokinetic parameters between patients with ischaemic heart disease and healthy volunteers. In addition, dofetilide pharmacokinetics were independent of NYHA classification of heart failure, left ventricular ejection fraction or underlying heart disease (e.g. angina, congestive heart failure, myocardial infarction).

Elderly: Apparent clearance was significantly lower and plasma concentrations 25% higher in elderly (>65 years) compared to young healthy volunteers. However, this reduced clearance is accounted for primarily by a reduction in renal function which occurs in the elderly and any dosage adjustment should be made on the basis of creatinine clearance (see section 4.2).

Female patients: Female patients have approximately 12-18% lower dofetilide clearances (approximately 14-22% higher dofetilide levels) compared to men. In females, as in males, renal function was the single greatest factor influencing dofetilide clearance. (see section 4.2).

5.3 Preclinical safety

Testicular atrophy: Repeat dose studies of 24 months duration in mice and 12 months duration in rats and dogs indicate that dofetilide is associated with testicular atrophy in these species. The testicular atrophy was observed only at exposures considered to be sufficiently in excess of the maximum human systemic exposure, indicating little relevance to clinical use. The effects are considered to be a direct pharmacological action since no changes have been observed in hormones related to testicular function in rats or man.

Reproductive toxicology: Dofetilide has been shown to be embryotoxic and teratogenic in rats and embryotoxic in mice. In these animals, the systemic exposure at which these effects were seen are respectively 6- and 2-fold greater than the maximum recommended clinical exposure. Dofetilide does not impair fertility when administered to male or female rats using an oral dose of 1mg/kg/day or an intravenous dose of 4 mg/kg/day. The intravenous dose used in these studies corresponds to systemic exposure multiples of 34 compared to the maximum recommended clinical dose. The dose used in oral fertility studies was chosen in order to avoid embryolethality in pregnant females.
Carcinogenicity and genotoxicity:
Dofetilide does not cause carcinogenic effects when administered to mice or rats and shows no evidence of genotoxicity.
6. **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

**Capsules:**
- Microcrystalline cellulose
- Maize starch
- Colloidal anhydrous silica
- Magnesium stearate

**Capsule Shell:**
- Gelatin
- Titanium dioxide (E171)
- FD&C Yellow 6 (E110)
- Black ink containing black iron oxide (E172), shellac, soya lecithin and anti-foam DC 1510

6.2 **Incompatibilities**

Not applicable

6.3 **Shelf Life**

2 years.

6.4 **Special precautions for storage**

Do not store above 30°C

6.5 **Nature and content of container**

High density polyethylene bottles containing 200 capsules with child-resistant, lined polypropylene caps or lined metal caps.

Aclar blisters containing 14, 28, 56 or 100 capsules per carton.

6.6 **Instructions for use and handling**

No special requirements.

7. **MARKETING AUTHORISATION HOLDER**

Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ, UK

8. **NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS**

9. **DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION**

10. **DATE OF REVISION OF THE TEXT**
1. NAME OF THE MEDICINAL PRODUCT

TIKOSYN 500 microgram hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 500 micrograms of dofetilide

3. PHARMACEUTICAL FORM

Capsules, hard

TIKOSYN 500 microgram capsules are peach and white and are marked with TKN 500 PFIZER

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tikosyn is a Class III antiarrhythmic agent that is indicated for the following:

(i) Conversion of persistent atrial fibrillation or atrial flutter to normal sinus rhythm in patients in whom cardioversion by electrical means is not appropriate and in whom the duration of the arrhythmic episode is less than 6 months (see section 5.1).

(ii) Maintenance of sinus rhythm (after conversion) in patients with persistent atrial fibrillation or atrial flutter. Because TIKOSYN can cause ventricular arrhythmias, it should be reserved for patients in whom atrial fibrillation/atrial flutter is highly symptomatic and in whom other antiarrhythmic therapy is not appropriate.

Dofetilide has **not** been shown to be effective in patients with paroxysmal atrial arrhythmias (including paroxysmal atrial fibrillation).

4.2 Posology and Method of Administration

- During treatment with TIKOSYN, patients must be managed by a specialist experienced in the treatment of arrhythmias.
- Therapy with TIKOSYN must be initiated in an in-patient setting that provides continuous ECG monitoring. Patients should be monitored for at least the first three days (72 hours) of TIKOSYN therapy and for at least 12 hours after electrical or pharmacological conversion.
- TIKOSYN capsules can be taken with or without food.
- The dose of TIKOSYN must be individualised for every patient according to calculated creatinine clearance, cardiac status (see below) and QTc.

Measurement of QT Interval:

Prior to administration of the first dose, the QTc must be determined using an average of 5-10 beats. For patients with a heart rate greater than 60 beats per minute, QTc is calculated using Bazett’s formula as follows: QTc = QT / √RR. However, if the heart rate is less than 60 bpm,
QT (not QTc) interval should be used. If the QTc (or QT interval as appropriate) is greater than 440 msec (or 500 msec in patients with ventricular conduction abnormalities), TIKOSYN is contraindicated.

**Calculation of Creatinine Clearance**

Prior to the administration of the first dose the patient’s creatinine clearance must be calculated. This is calculated from serum creatinine (μmol/l) using the following formula:

\[
\text{creatinine clearance (}\text{male}) = \frac{(140-\text{age}) \times \text{body weight in kg} \times 1.22}{\text{serum creatinine (μmol/l)}} \text{ ml/min}
\]

\[
\text{creatinine clearance (}\text{female}) = \frac{(140-\text{age}) \times \text{body weight in kg} \times 1.04}{\text{serum creatinine (μmol/l)}} \text{ ml/min}
\]

When serum creatinine is in mg/dl, the calculated value obtained must be multiplied by 88.4 (1 mg/dl = 88.4 μmol/l) to determine the creatinine clearance.

**Dose regimen**

- The maximum recommended dose is 500 micrograms twice daily for patients with normal renal function and normal cardiac status. Patients with symptomatic heart failure or recent myocardial infarction (MI), with left ventricular dysfunction (ejection fraction (EF) \(\leq 35\%\)) should **not** receive doses in excess of 250 micrograms twice daily.
- TIKOSYN must only be dosed according to the flow chart, taking into account the patient’s baseline QTc, creatinine clearance and cardiac status (see below).

**Starting dose for conversion and maintenance**

TIKOSYN is contraindicated when the baseline QTc interval is >440 msec.

In patients with baseline QTc \(\leq 440\) msec, the starting dose of TIKOSYN is summarised below and is detailed in the following flow chart:

<table>
<thead>
<tr>
<th>Calculated creatinine clearance:</th>
<th>Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60 ml/min</td>
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</tr>
<tr>
<td>(&gt;40)(\leq 60) ml/min</td>
<td>250 micrograms twice daily</td>
</tr>
<tr>
<td>(\geq 20)(\leq 40) ml/min</td>
<td>125 micrograms twice daily</td>
</tr>
<tr>
<td>&lt; 20 ml/min</td>
<td>Dofetilide is contraindicated in these patients.</td>
</tr>
</tbody>
</table>

Other patients

<table>
<thead>
<tr>
<th>Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 micrograms twice daily</td>
</tr>
<tr>
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</tr>
<tr>
<td>250 micrograms twice daily</td>
</tr>
<tr>
<td>125 micrograms twice daily</td>
</tr>
<tr>
<td>Dofetilide is contraindicated in these patients.</td>
</tr>
</tbody>
</table>

31
Place Patient on continuous ECG monitoring

Check baseline QTc
If QTc >440msec, do not use TIKOSYN
If QTc ≤ 440msec, proceed

Calculate creatinine clearance (CLcr)

If CLcr <20 ml/min, dofetilide is CONTRAINDICATED

If CLcr is >60 ml/min, assess cardiac status

If patients have symptomatic CHF or recent MI, with EF ≤ 35%, start with 250 micrograms twice daily

For other patients start with 500 micrograms twice daily

If CLcr is 40-60 ml/min, start with 250 micrograms twice daily
If CLcr is 20-<40 ml/min, start with 125 micrograms twice daily

2-3 hours after the first dose check the QTc

(Post first dose only) If increase in QTc is ≤15%, continue current dose

(Post first dose only) If increase in QTc is >15% or QTc is >500 msec, Decrease The Dose:
if 500 micrograms BID, reduce to 250 micrograms BID
if 250 micrograms BID, reduce to 125 micrograms BID
if 125 micrograms BID, reduce to 125 micrograms OD

QTc must be determined 2-3 hours after each in-patient dose. If at any time after the second dose QTc increases above 500 msec dofetilide should be discontinued
Special Considerations

Switch to TIKOSYN capsules from Class I or other Class III antiarrhythmic therapy
Before initiating TIKOSYN capsules, previous Class I or Class III antiarrhythmic therapy should be withdrawn for a minimum of 3 plasma half-lives. Due to the unpredictable pharmacokinetics of amiodarone, TIKOSYN capsules should not be initiated following amiodarone therapy until amiodarone plasma levels are below 0.3 μg/ml or after amiodarone has been withdrawn for three months.

Cardioversion
The minimum monitoring period after initiation of TIKOSYN therapy is 72 hours. If patients do not convert to normal sinus rhythm within 24 hours of initiation, electrical cardioversion should be re-considered. If a patient converts to normal sinus rhythm towards the end of the monitoring period, monitoring should be continued for at least 12 hours after electrical or pharmacological cardioversion.

Maintenance of TIKOSYN Therapy
The usual maintenance dose is the dose effective in converting the arrhythmia to sinus rhythm. Renal function and QTc should be re-evaluated every three months or as medically warranted. Any deterioration of renal function should result in downwards adjustment of the TIKOSYN dose (refer to the table above). If QTc exceeds 500 milliseconds (or 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.

Dose Adjustment
In patients with multiple risk factors for proarrhythmia (see Section 4.4, proarrhythmia), it may be appropriate to consider using a maximum dose of 250 micrograms twice daily, adjusted for creatinine clearance and QT interval where required. It is critically important that if at any time the dose of TIKOSYN is increased, the patient must be rehospitalised for at least three days. Previous toleration of higher doses does not exclude the need for rehospitalisation.

Missed doses
If a patient misses a dose, patients should be instructed NOT to double the next dose. The next dose is to be taken at the usual time. If more than one dose is missed, patients should contact their physician as soon as possible; hospitalisation for re-initiation of therapy may be required.

Use in patients with renal impairment
Dofetilide is excreted primarily via the renal route. Therefore, in patients with renal impairment, dosage should be adjusted as described above (see sections 4.2, 4.3 and 5.2).

Use in patients with hepatic impairment
No dosage adjustment is required for patients with mild or moderate hepatic impairment (Child-Pugh Class A and B). Dofetilide is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C) (see sections 4.3 and 5.2).

Use in children
The use of TIKOSYN in children under 18 years is contraindicated (see sections 4.3 and 5.3).

Use in the elderly
No additional change to dosage needs to be made for elderly patients. (see section 5.2).

Use in female patients
The recommended dose is the same for male and female patients (see section 5.2).

4.3 Contraindications

TIKOSYN is contraindicated in patients:

- with congenital or acquired long QT syndromes.
- with a known hypersensitivity to dofetilide or any of the excipients of the product.
- with baseline (pre-treatment) QTc greater than 440 msec (or 500 msec in patients with ventricular conduction abnormalities)
- with severe renal impairment (creatinine clearance <20 ml/min), including patients on dialysis
- with severe hepatic impairment
- with second or third degree AV block or sick sinus syndrome (unless a functioning pacemaker is in situ)
- with bradycardia (less than 50 bpm)
- with hypokalaemia
- under the age of 18

In addition, TIKOSYN is contraindicated in combination with the following medications: (see section 4.5):

- cimetidine
- verapamil
- ketoconazole
- QT prolonging drugs (including Class I and other Class III antiarrhythmic agents)
- drugs that inhibit the renal cation transport system (trimethoprim, megestrol and prochlorperazine)
- CYP3A4 inhibitors (e.g. azole antifungal agents, macrolide antibiotics and protease inhibitors)

4.4 Special warnings and special precautions for use

Anticoagulation:
Patients with atrial fibrillation should be anticoagulated according to standard medical practice prior to electrical or pharmacological cardioversion. Anticoagulant therapy may be continued after cardioversion according to standard medical practice.

Proarrhythmia:
Torsade de Pointes, a polymorphic form of ventricular tachycardia, is the most common manifestation of proarrhythmia with dofetilide.

In general, the following are risk factors for Torsade de Pointes: renal impairment, structural heart disease, prolonged QT interval, a low cardiac ejection fraction, bradycardia and/or abnormal plasma levels of potassium or magnesium. Hypokalemia must be corrected before initiation of TIKOSYN therapy and the dose of TIKOSYN should be adjusted according to calculated creatinine clearance and QTc as described above. The risk of proarrhythmia is greater in female patients compared to males. During the TIKOSYN clinical programme, the relative risk for Torsade de Pointes was approximately 3 fold greater in females compared to males; however, there was no increased mortality risk in females taking TIKOSYN compared to placebo.

Patients with ventricular arrhythmias:
A higher incidence of Torsade de Pointes has been observed in patients with atrial fibrillation and concomitant ventricular arrhythmias.
Digoxin: The concomitant administration of digoxin with dofetilide was associated with a higher occurrence of Torsade de Pointes. Therefore, these patients should be treated with caution.

Heart failure: Although dofetilide does not depress cardiac performance, the risk of proarrhythmia in patients with chronic heart failure is higher than in patients without heart failure. Experience with the use of dofetilide in severe cardiac failure (NYHA class IV) is limited. Therefore, these patients should be treated with caution and they should be carefully supervised.

If proarrhythmia occurs, TIKOSYN therapy should be discontinued. Management of Torsade de Pointes may include electrical cardioversion, temporary cardiac pacing or treatment with isoprenaline or magnesium sulphate infusion.

Renal Impairment: Dosage adjustment is required based on creatinine clearance (see sections 4.2, 4.3 and 5.2).

4.5 Interactions with other medicinal products and other forms of interaction

Contraindicated combinations

Cimetidine: Concomitant administration of cimetidine with TIKOSYN is contraindicated. Cimetidine dosing at 400mg twice daily has been shown to increase plasma levels of dofetilide by 58%. Cimetidine doses of 100mg twice daily resulted in a 13% increase in dofetilide plasma levels. Therefore an alternative agent to cimetidine should be used (ranitidine, omeprazole, or antacids).

Verapamil: Concomitant use of verapamil with TIKOSYN is contraindicated. Co-administration of dofetilide with verapamil resulted in transient increases in dofetilide peak plasma levels of 43%, although overall exposure to dofetilide was not significantly increased. TIKOSYN does not affect the pharmacokinetics or pharmacodynamics of verapamil.

Ketoconazole: Concomitant use of ketoconazole is contraindicated. Ketoconazole at 400mg daily co-administered with dofetilide has been shown to increase dofetilide exposure by 55%.

QT Interval Prolonging Drugs: The co-administration of TIKOSYN with drugs known to prolong the QT interval has not been studied and is contraindicated due to the possible potentiation of the pharmacodynamic effects of dofetilide (see Section 4.3). Examples include certain neuroleptics, cisapride, bepridil, tricyclic antidepressants, certain antihistamine drugs (e.g. H₁ receptor antagonists) and certain macrolide antibiotics (e.g. erythromycin).

CYP3A4 Inhibitors: Dofetilide is not an inhibitor of CYP3A4 nor of other cytochrome P450 isoenzymes (CYP2C9, CYP2D6). Dofetilide is metabolised by the CYP3A4 isoenzyme of the P450 cytochrome system. However, it has a low affinity for this isoenzyme. Inhibitors of this isoenzyme could potentially increase systemic dofetilide exposure. Therefore these drugs are contraindicated in combination with TIKOSYN (see section 4.3). CYP3A4 inhibitors include: macrolide antibiotics (e.g. erythromycin), azole antifungal agents (e.g. ketoconazole) and protease inhibitors (e.g. ritonavir).

Clinically significant interactions

Inhibitors of renal cation secretion: Dofetilide is eliminated by renal cation secretion. The magnitude of the effect that cimetidine and ketoconazole have on the renal clearance of dofetilide suggests that these drugs are contraindicated in combination with TIKOSYN.
Renal cation transport inhibitors include: trimethoprim, prochlorperazine and megestrol. Azole antifungal agents (e.g. itraconazole) may also inhibit renal transport of dofetilide. In addition, caution should be taken when drugs that are actively secreted via this route are co-administered with dofetilide e.g. triamterene, metformin and amiloride.

Use with Class I and Class III antiarrhythmic agents: The use of dofetilide in conjunction with other antiarrhythmic drugs that prolong the QT interval has not been studied but is contraindicated due to the possible potentiation of the pharmacodynamic effects of dofetilide (see section 4.3). Class I or class III agents should be withheld for at least three half-lives prior to dosing with dofetilide. In clinical trials, TIKOSYN was only administered to patients previously treated with amiodarone if amiodarone levels were below 0.3 μg/ml or after amiodarone had been withdrawn for three months (see section 4.2).

Potassium-depleting diuretics: Hypokalaemia or hypomagnesaemia may occur with administration of potassium-depleting diuretics, increasing the potential for Torsade de Pointes. Potassium levels should be within the normal range prior to administration of TIKOSYN and maintained in the normal range during administration of TIKOSYN.
Other drug interaction information

Studies in healthy volunteers have shown that dofetilide does not affect the pharmacokinetics or pharmacodynamics of concomitant medications such as: warfarin, digoxin, propranolol, phenytoin, theophylline and oral contraceptives.

In healthy volunteers, amlodipine, phenytoin, glibenclamide, ranitidine, omeprazole, hormone replacement therapy (a combination of conjugated oestrogens and medroxyprogesterone), antacid (aluminium and magnesium hydroxide) and theophylline did not affect the pharmacokinetics of dofetilide.

In a population pharmacokinetic analysis of 1445 patients, drugs in the following groups were shown to have no clinically significant interaction with dofetilide: ACE inhibitors, oral anticoagulants, calcium channel blockers, beta blockers, cardiac glycosides, inducers of cytochrome P450 3A4, substrates and inhibitors of cytochrome P450 3A4, substrates and inhibitors of P-glycoprotein, sulphonylureas, nitrates, loop diuretics, potassium sparing diuretics, substrates of tubular cation transport, and QT prolonging drugs. Differences in clearance between patients on these medications and those off these medications varied between -16% and +3%. The mean clearances of dofetilide was 16% and 15% lower in patients taking thiazide diuretics and inhibitors of tubular organic cation transport, respectively. However see section 4.3 Contraindications.

Food: The bioavailability of dofetilide is not affected by the concomitant ingestion of food although the time to maximum plasma concentration is prolonged to 3-4 hours.

4.6 Pregnancy and lactation

For TIKOSYN no clinical data on exposed pregnancies are available. Studies in animals have shown reproductive toxicity (see section 5.3). The relevance of these data for humans is unknown; therefore TIKOSYN should not be used during pregnancy unless clearly necessary.

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

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic profile and clinical experience, there is no evidence to suggest that dofetilide affects the ability to drive or use machines.

4.8 Undesirable effects

Dofetilide has been administered to more than 5000 subjects in clinical trials.

The most serious dose related undesirable effect with TIKOSYN is Torsade de Pointes. This is the most common manifestation of proarrrhythmia that is observed in association with QT-prolonging drugs including dofetilide. The overall incidence of Torsade de Pointes observed in patients with supraventricular arrhythmia was 0.8% (11/1346). In the DIAMOND CHF population (see section 5.1) the incidence of Torsade de Pointes was 3.3% (25/762) and in DIAMOND MI it was 0.9% (7/749). The majority of Torsade de Pointes episodes occurred within the first three days of TIKOSYN therapy.

In addition, the following undesirable effects have been observed in patients being treated for supraventricular arrhythmias at the recommended clinical dose. The placebo-corrected incidence is shown in brackets.

Body as a whole: asthenia (0.4%), headache (1.1%)
Digestive: nausea (0.6%)
Nervous system: dizziness (0.5%)
Respiratory: dyspnoea (0.5%)

Increases in eosinophil and monocyte counts and low plasma magnesium levels have been reported in patients receiving dofetilide. Mild elevations of serum transaminases have been seen in clinical studies, although at the recommended dose of dofetilide the incidence was similar to placebo-treated patients. Rare cases of thrombocytopenia have been observed in clinical studies although a causal relationship to dofetilide has not been established.

4.9 Overdose

The most prominent manifestation of overdosage is likely to be excessive prolongation of the QTc interval and the occurrence of Torsade de Pointes.

In cases of overdose when QTc interval exceeds 500 msec (or 550 msec in patients with ventricular conduction abnormalities) cardiac monitoring should be initiated in hospital. Close medical monitoring and supervision should continue until the QTc interval returns to baseline levels. There is no known antidote to dofetilide, therefore treatment of overdose should be symptomatic and supportive. Charcoal slurry may be given soon after overdosing but has only been seen to be useful when given within 15 minutes of dofetilide administration (T_{max} is 2-3 hours).

Experience has shown that administration of isoprenaline infusion, with or without cardiac pacing is effective in treating prolongation of the QTc interval. Administration of intravenous magnesium sulphate may also be effective in the management of Torsade de Pointes. In vitro studies have shown that dofetilide is only slowly removed by dialysis; therefore this treatment is unlikely to be useful in the management of acute overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiarrhythmics
ATC code: C01BD04

Mechanism of action:
Dofetilide is a highly selective Class III antiarrhythmic agent (according to the Vaughan Williams classification) and blocks a single cardiac potassium channel (I_{Kr}). At clinically relevant concentrations dofetilide does not have any effect on sodium channels (associated with Class I effects), calcium channels (associated with Class IV effects) or other potassium channels and has no beta blocking (Class II) or alpha-adrenergic blocking activity.

Electrophysiology and haemodynamics:
Dofetilide has no negative inotropic effects in patients with normal or with severely impaired left ventricular function. Dofetilide causes a reduction in heart rate (4-8 beats per minute) and has no effect on conduction velocity, blood pressure, PR interval or QRS width.

Dofetilide selectively prolongs the QT interval of the ECG, the monophasic action potential duration and the effective refractory period in a concentration dependent manner in volunteers. In animal models the atria have been shown to be more sensitive to the effects of dofetilide than the ventricles.

Pharmacokinetic - pharmacodynamic relationship:
In healthy volunteers and in patients with supraventricular or ventricular tachyarrhythmias, ischaemic heart disease or renal impairment, the relationship between dofetilide plasma levels and prolongation of QTc was linear. The maximum prolongation of QTc was usually observed during days 2-3 of therapy.

**Further information on clinical studies:**
Dofetilide has been administered to a total of more than 3400 patients for a mean duration of over 9 months for the treatment of supraventricular and ventricular arrhythmias.

Dofetilide was significantly superior to placebo in converting patients from atrial fibrillation and/or atrial flutter to normal sinus rhythm. In two clinical studies, conversion rates were 30% for patients receiving dofetilide compared to 1% for placebo. As with other therapies, factors associated with improved likelihood of conversion to normal sinus rhythm include patients presenting with atrial flutter (as opposed to atrial fibrillation) and normal to moderately enlarged left atrial diameter (as opposed to severely enlarged left atrium). In clinical studies, the conversion rate was 56% for atrial flutter and 26% for atrial fibrillation.

In the two pivotal studies in patients with atrial fibrillation/atrial flutter, dofetilide was associated with a statistically significant increase in the number of patients maintained in normal sinus rhythm following electrical cardioversion or conversion with dofetilide when compared to placebo-treated patients. At the recommended dose, the probability of remaining in sinus rhythm in the two studies after 6 months was 62% and 71% whereas the equivalent probability for placebo-treated patients was 37% and 26% respectively.

In patients with supraventricular arrhythmias, dofetilide converts and maintains sinus rhythm which is associated with a reduction in frequency and severity of arrhythmia-induced symptoms (shortness of breath and palpitations), an increased exercise tolerance and an improvement in quality of life. In a pooled analysis of patients with supraventricular arrhythmias, survival rates in patients treated with dofetilide and placebo were comparable.

**DIAMOND survival studies:** Dofetilide was administered to 1511 patients for up to 3 years in the DIAMOND (Danish Investigations of Arrhythmia and Mortality on Dofetilide) studies. These studies recruited patients with compromised left ventricular function (ejection fraction ≤ 35%) in addition to having either symptomatic heart failure (DIAMOND CHF) or a recent myocardial infarction (DIAMOND MI) within the previous 7 days. Patients in the DIAMOND CHF study, when treated with dofetilide, had a one year survival of 73% compared to 72% in placebo-treated patients. In addition, dofetilide reduced the incidence of hospitalisations in patients with worsening congestive heart failure with one year event-free survival of 71% on dofetilide and 60% on placebo. DIAMOND MI showed that for patients with recent myocardial infarction, survival after 1 year was 79% for patients taking dofetilide compared to 77% on placebo. These data show that dofetilide was not associated with an increased risk of mortality in patients with CHF or following recent MI.

**Other studies:** Dofetilide reduces the defibrillation threshold in patients undergoing implantation of a cardioverter defibrillator device (ICD) and can be used safely in patients with ICDs.

5.2 Pharmacokinetic properties

**Absorption:** In healthy subjects, the oral bioavailability of dofetilide is >90%. Maximum observed plasma concentrations occur at about 2-3 hours in the fasted state.

Bioavailability is unaffected by food or antacid. Steady state plasma concentrations are attained within 2-3 days and can be predicted from a single dose. Over the clinical dose
range, plasma concentrations increase in a predictable, linear fashion with dose. Variability in plasma concentrations within and between subjects is low.

**Distribution:** Plasma protein binding of dofetilide is 60-70% and is independent of plasma concentration. Plasma protein binding of dofetilide is unaffected by renal impairment. Mean volume of distribution is approximately 3 L/kg and is linearly correlated with body weight.

**Metabolism:** Metabolism is a minor component of dofetilide elimination. *In vitro* studies with human liver microsomes show that dofetilide is predominantly metabolised by the cytochrome P450 isoenzyme, CYP3A4; however it has a low affinity for this isoenzyme. Metabolites are formed by N-dealkylation and N-oxidation. There are no quantifiable metabolites circulating in plasma.

**Elimination:** The terminal half-life is approximately 10 hours. Approximately 80% of a single dose of dofetilide is excreted in urine. Seventy percent of dofetilide is excreted unchanged in urine with the remainder converted to metabolites. Renal elimination involves both glomerular filtration and active cation secretion (which can be inhibited by cimetidine and ketoconazole).

**Pharmacokinetics in special groups**

**Renal impairment:** In volunteers with varying degrees of renal impairment and patients with arrhythmias there is a linear relationship between clearance of dofetilide and creatinine clearance. In clinical studies the half-life of dofetilide in subjects with low creatinine clearance was also extended. Thus, dosage adjustment is required based on creatinine clearance (see section 4.2).

**Hepatic impairment:** There was no clinically significant alteration in the pharmacokinetics of dofetilide in volunteers with mild to moderate hepatic impairment (Child-Pugh Class A and B) compared to age and weight matched healthy volunteers. Patients with severe hepatic impairment (Child-Pugh Class C) were not studied. (see section 4.2)

**Patients with arrhythmias:** Population pharmacokinetic analyses of dofetilide given orally indicate that the plasma concentrations are similar between patients treated for supraventricular arrhythmias or ventricular tachycardia and normal healthy volunteers, after adjustment has been made for renal function.

**Patients with heart disease:** Studies with intravenously administered dofetilide showed that there was no difference in pharmacokinetic parameters between patients with ischaemic heart disease and healthy volunteers. In addition, dofetilide pharmacokinetics were independent of NYHA classification of heart failure, left ventricular ejection fraction or underlying heart disease (e.g. angina, congestive heart failure, myocardial infarction).

**Elderly:** Apparent clearance was significantly lower and plasma concentrations 25% higher in elderly (>65 years) compared to young healthy volunteers. However, this reduced clearance is accounted for primarily by a reduction in renal function which occurs in the elderly and any dosage adjustment should be made on the basis of creatinine clearance (see section 4.2).

**Female patients:** Female patients have approximately 12-18% lower dofetilide clearances (approximately 14-22% higher dofetilide levels) compared to men. In females, as in males, renal function was the single greatest factor influencing dofetilide clearance. (see section 4.2).
5.3 Preclinical safety

Testicular atrophy:
Repeat dose studies of 24 months duration in mice and 12 months duration in rats and dogs indicate that dofetilide is associated with testicular atrophy in these species. The testicular atrophy was observed only at exposures considered to be sufficiently in excess of the maximum human systemic exposure, indicating little relevance to clinical use. The effects are considered to be a direct pharmacological action since no changes have been observed in hormones related to testicular function in rats or man.

Reproductive toxicology:
Dofetilide has been shown to be embryotoxic and teratogenic in rats and embryotoxic in mice. In these animals, the systemic exposure at which these effects were seen are respectively 6- and 2-fold greater than the maximum recommended clinical exposure. Dofetilide does not impair fertility when administered to male or female rats using an oral dose of 1mg/kg/day or an intravenous dose of 4 mg/kg/day. The intravenous dose used in these studies corresponds to systemic exposure multiples of 34 compared to the maximum recommended clinical dose. The dose used in oral fertility studies was chosen in order to avoid embryolethality in pregnant females.

Carcinogenicity and genotoxicity:
Dofetilide does not cause carcinogenic effects when administered to mice or rats and shows no evidence of genotoxicity.
6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsules:
- Microcrystalline cellulose
- Maize starch
- Colloidal anhydrous silica
- Magnesium stearate

Capsule Shell:
- Gelatin
- Titanium dioxide (E171)
- FD&C Yellow 6 (E110)
- Black ink containing black iron oxide (E172), shellac, soya lecithin and anti-foam DC 1510

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and content of container

High density polyethylene bottles containing 200 capsules with child-resistant, lined polypropylene caps or lined metal caps.

Aclar blisters containing 14, 28, 56 or 100 capsules per carton.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ, UK

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT
ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION
A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Pfizer S.A., B.P. 109-37401 Amboise Cedex, France

Manufacturing Authorisation issued on 2 May 1997 by Agence du Medicament Direction de l’inspection et des etablissements (143-147, Boulevard Anatole France-93200 Saint Denis, France)

B. CONDITIONS OF THE MARKETING AUTHORISATION

- CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORIZATION HOLDER

Medicinal product subject to restricted medical prescription
(See Annex I: Summary of Product Characteristics, 4.2).
ANNEX III
LABELLING AND PACKAGE LEAFLET
A. LABELLING
TIKOSYN 125 microgram hard capsules
Dofetilide
dofetilide 125 micrograms
This product includes the colouring agent E110
14 hard capsules
Oral use.
Read the enclosed leaflet before use.
Keep out of the reach and sight of children
Expiry date: {month/year}
Do not store above 30°C. Keep capsules in original package in order to protect from moisture
Pfizer Limited
Sandwich
Kent, CT13 9NJ, UK
EU/0/00/000/000
Batch number: {number}
Medicinal product subject to medical prescription
TIKOSYN 125 microgram hard capsules
Dofetilide
dofetilide 125 micrograms
This product includes the colouring agent E110
28 hard capsules
Oral use.
Read the enclosed leaflet before use.
Keep out of the reach and sight of children
Expiry date: {month/year}

Do not store above 30°C. Keep capsules in original package in order to protect from moisture

Pfizer Limited
Sandwich
Kent, CT13 9NJ, UK

EU/0/00/000/000

Batch number: {number}

Medicinal product subject to medical prescription
TIKOSYN 125 microgram hard capsules
Dofetilide
dofetilide 125 micrograms
This product includes the colouring agent E110
56 hard capsules
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Read the enclosed leaflet before use.
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Batch number: {number}
Medicinal product subject to medical prescription
TIKOSYN 250 microgram hard capsules
Dofetilide

Pfizer Limited

Expiry date: {month/year}

Batch number: {number}
TIKOSYN 500 microgram hard capsules
Dofetilide
dofetilide 500 micrograms
This product includes the colouring agent E110
14 hard capsules
Oral use.
Read the enclosed leaflet before use.
Keep out of the reach and sight of children
Expiry date: {month/year}
Do not store above 30°C. Keep capsules in original package in order to protect from moisture

Pfizer Limited
Sandwich
Kent, CT13 9NJ, UK

EU/0/00/000/000

Batch number: {number}

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Keep out of the reach and sight of children
Expiry date: {month/year}
Do not store above 30°C. Keep capsules in original package in order to protect from moisture
Pfizer Limited
Sandwich
Kent, CT13 9NJ, UK
EU/0/00/000/000
Batch number: {number}
Medicinal product subject to medical prescription
TIKOSYN 500 microgram hard capsules
Dofetilide
dofetilide 500 micrograms
This product includes the colouring agent E110
56 hard capsules
Oral use.
Read the enclosed leaflet before use.
Keep out of the reach and sight of children
Expiry date: {month/year}
Do not store above 30°C. Keep capsules in original package in order to protect from moisture
Pfizer Limited
Sandwich
Kent, CT13 9NJ, UK
EU/0/00/000/000
Batch number: {number}
Medicinal product subject to medical prescription
TIKOSYN 500 microgram hard capsules
Dofetilide
dofetilide 500 micrograms
This product includes the colouring agent E110
100 hard capsules
Oral use.
Read the enclosed leaflet before use.
Keep out of the reach and sight of children
Expiry date: {month/year}
Do not store above 30°C. Keep capsules in original package in order to protect from moisture
Pfizer Limited
Sandwich
Kent, CT13 9NJ, UK
EU/0/00/000/000
Batch number: {number}
Medicinal product subject to medical prescription
TIKOSYN 500 microgram hard capsules
Dofetilide
dofetilide 500 micrograms
This product includes the colouring agent E110
200 hard capsules
Oral use.
Read the enclosed leaflet before use.
Keep out of the reach and sight of children
Expiry date: {month/year}
Do not store above 30°C. Keep capsules in original package in order to protect from moisture
Pfizer Limited
Sandwich
Kent, CT13 9NJ, UK
EU/0/00/000/000
Batch number: {number}
Medicinal product subject to medical prescription
TIKOSYN 500 microgram hard capsules
Dofetilide

Pfizer Limited

Expiry date: {month/year}

Batch number: {number}
B. PACKAGE LEAFLET
In this leaflet:
1. What TIKOSYN is and what it is used for
2. Before you take TIKOSYN
3. How to take TIKOSYN
4. Possible side effects
5. Storing TIKOSYN

TIKOSYN 125 microgram hard capsules
(dofetilide)
- The active substance is dofetilide
- The other ingredients are: microcrystalline cellulose, maize starch, colloidal anhydrous silica, magnesium stearate, gelatin, titanium dioxide (E171), FD&C Yellow 6 (E110), black ink containing black iron oxide (E172), shellac, soya lecithin and anti-foam DC 1510.

The licence to market TIKOSYN is held by:
Pfizer Limited, Sandwich, Kent, CT13 9NJ, UK.

TIKOSYN is made by:
Pfizer S.A., Zone Industrielle de Pocé-sur-Cisse, 37401 Amboise Cedex, France.

1. WHAT TIKOSYN IS AND WHAT IT IS USED FOR

TIKOSYN is presented as hard capsules containing 125 micrograms of dofetilide per capsule.
TIKOSYN belongs to a group of medicines called antiarrhythmics. These medicines are used to control an irregular or rapid heartbeat.

TIKOSYN is taken to control the rhythm of the heart.
It is used in people whose hearts beat irregularly or too fast. These conditions are called arrhythmias. An abnormal heartbeat reduces the ability of the heart to pump blood around the body. This condition may cause palpitations or an uncomfortable feeling in the chest, breathlessness, tiredness, dizziness, faintness, and anxiety. TIKOSYN relieves symptoms by helping the heart to beat normally.
TIKOSYN has been prescribed for you. Do not allow anyone else to take it.

2. BEFORE YOU TAKE TIKOSYN

Do not take TIKOSYN:
- if you are hypersensitive (allergic) to dofetilide or any of the other ingredients of TIKOSYN, in particular FD&C Yellow 6 (E110).
- if you have one of the following heart conditions
congenital or acquired long QT syndrome
sick sinus syndrome or heart block without a pacemaker
- if you have severe liver or kidney disease or are on kidney dialysis
- if you have a slow heartbeat
- if you are under the age of 18
- if you have low blood salts

It is extremely important that you inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those that are obtained without a prescription. Some medicines may affect the way that TIKOSYN works. A list of the medicines that may affect TIKOSYN is shown below in the section ‘Taking other medication with TIKOSYN’. However, the following medicines must never be taken during your course of TIKOSYN treatment:

- Cimetidine (a medicine for treating stomach ulcers)
- Verapamil (a medicine for treating angina, high blood pressure or an irregular heart beat)
- Some medicines used to treat fungal infections, such as ketoconazole or itraconazole
- Other drugs to control your heart rhythm
- Cisapride (a medicine for stomach problems)
- Bepridil
- Medicines for the treatment of mental conditions, such as prochlorperazine
- Certain antidepressants and certain neuroleptics
- Medicines for allergies or hay fever (antihistamines)
- Certain antibiotics, such as erythromycin and trimethoprim
- Megestrol
- Medicines to treat AIDS (protease inhibitors), such as ritonavir

**Take special care with TIKOSYN:**

In a small number of people (less than one in a hundred), dofetilide may make the heart beat irregularly, causing you to feel dizzy or have palpitations. If this happens, it is most likely to occur during the first few days of treatment. This is why the doctor has monitored your heart carefully and has made sure the medicine is working properly

If you have palpitations, or feel faint or dizzy, you must seek urgent medical advice before taking your next TIKOSYN capsule.

If you experience prolonged diarrhoea, sweating, thirst or vomiting, you must tell your doctor as these conditions can change the balance of salts in your body and affect the way that TIKOSYN works.

Before you started your TIKOSYN treatment, your doctor will have worked out which dose is right for you. If you answered ‘Yes’ to any of the following questions, your doctor may have decided to give you a lower dose or special care:
- Have you ever had any kidney problems?
- Have you ever had any other heart problem?

You must tell your doctor if you are taking any other medicines for any reason as these may interfere with the way TIKOSYN works.

**Taking TIKOSYN with food and drink:**
TIKOSYN can be taken with or without food. You should swallow the whole capsule with a glass of water.
**Pregnancy**
TIKOSYN should not be taken during pregnancy. Contact your doctor if you become pregnant while taking TIKOSYN.

**Breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines:**
TIKOSYN does not affect your ability to drive or use machines.

**Important information about some of the ingredients of TIKOSYN:**
You should not take TIKOSYN if you are allergic to the colouring agent FD&C Yellow 6 (E110).

**Taking other medicines with TIKOSYN:**
It is extremely important that you inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those that are obtained without a prescription.

Some medicines, when taken at the same time as TIKOSYN, may change the effects of TIKOSYN. Discuss with your doctor if you take or have taken any of the medicines listed below:
- Cimetidine (a medicine for treating stomach ulcers).
- Verapamil (a medicine for treating angina, high blood pressure or an irregular heart beat).
- Cisapride (a medicine for stomach problems).
- Bepridil.
- Metformin (a medicine taken to treat diabetes)
- Some medicines used to treat fungal infections, such as ketoconazole or itraconazole
- Other drugs to control your heart rhythm
- Medicines for the treatment of mental conditions such as prochlorperazine
- Some diuretics (water tablets) such as triamterene or amiloride
- Certain antidepressants and certain neuroleptics
- Medicines for allergies or hay fever (antihistamines)
- Certain antibiotics, such as erythromycin and trimethoprim.
- Megestrol
- Medicines to treat AIDS (protease inhibitors), such as ritonavir

If you go into hospital or are prescribed another medicine, you must tell your doctor that you are taking TIKOSYN.

Always carry a list of all the medicines you are taking. If you have to go to the hospital or are treated by other doctors or dentists, tell them that you are taking TIKOSYN and show them a list of the medicines you are taking. They need this information to make sure your medicines are safe to take at the same time.

3. **HOW TO TAKE TIKOSYN**

Always follow your doctor’s instructions.

The usual dose of TIKOSYN is 500 micrograms of dofetilide, taken twice daily with approximately 12 hours between each dose. It is very important that you regularly take the
exact dose of TIKOSYN that your doctor has prescribed for you and that you never take an extra dose of TIKOSYN.

Lower doses (250 micrograms twice daily, 125 micrograms twice daily or 125 micrograms once daily) may be given to some people, for example those with reduced kidney function, some heart diseases or those who are sensitive to this type of medicine. When you started your treatment with TIKOSYN, your doctor will have monitored your heart and conducted some other tests. The results of these tests will have helped the doctor decide which dose of TIKOSYN is right for you. Do not change the dose for yourself.

It is important that you keep taking your medicine until your doctor tells you to stop. If you have palpitations, or feel faint or dizzy, you must seek urgent medical advice before taking your next TIKOSYN capsule. Your condition may get worse if you stop taking TIKOSYN.

If you take more TIKOSYN than you should:

If you take more capsules than prescribed, or if someone else takes your capsules, you must seek urgent medical advice or go to the nearest hospital casualty department immediately. Take your packet of TIKOSYN with you.

If you forget to take TIKOSYN:

It is important that you take your TIKOSYN capsules regularly. If you forget to take one capsule, take your next dose when it is due but never take a double dose to make up for the forgotten dose. If you forget to take more than one dose, contact your doctor before continuing your treatment.

4. POSSIBLE SIDE EFFECTS

Like all medicines, TIKOSYN can have side effects. Very rarely, TIKOSYN itself may cause rhythm disturbances of the heart (see section ‘Take special care with TIKOSYN’). You should contact your doctor urgently if you experience dizziness, palpitations or worsening of your symptoms. Other side effects may include weakness, headache, nausea, dizziness and breathlessness. Very rarely, cases of low blood platelet count and mild changes in liver function may occur. If you experience any of these side effects and they cause you concern, you should see your doctor.

If you notice any other unwanted effects not mentioned in this leaflet, please tell your doctor or pharmacist.

5. STORING TIKOSYN

Keep out of the reach and sight of children
Do not store above 30°C
Do not use after the expiry date stated on the carton

This leaflet was last approved on {date}
Further information
For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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France
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SE-183 25 TÄBY
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United Kingdom
Pfizer Limited
Ramsgate Rd
Sandwich, Kent
GB-CT13 9NJ
☎ +44 (0)1304 61 61 61
1. WHAT TIKOSYN IS AND WHAT IT IS USED FOR

TIKOSYN is presented as hard capsules containing 250 micrograms of dofetilide per capsule. TIKOSYN belongs to a group of medicines called antiarrhythmics. These medicines are used to control an irregular or rapid heartbeat.

TIKOSYN is taken to control the rhythm of the heart. It is used in people whose hearts beat irregularly or too fast. These conditions are called arrhythmias. An abnormal heartbeat reduces the ability of the heart to pump blood around the body. This condition may cause palpitations or an uncomfortable feeling in the chest, breathlessness, tiredness, dizziness, faintness, and anxiety. TIKOSYN relieves symptoms by helping the heart to beat normally. TIKOSYN has been prescribed for you. Do not allow anyone else to take it.

2. BEFORE YOU TAKE TIKOSYN

Do not take TIKOSYN:

- if you are hypersensitive (allergic) to dofetilide or any of the other ingredients of TIKOSYN, in particular FD&C Yellow 6 (E110).
- if you have one of the following heart conditions
congenital or acquired long QT syndrome
sick sinus syndrome or heart block without a pacemaker
- if you have severe liver or kidney disease or are on kidney dialysis
- if you have a slow heartbeat
- if you are under the age of 18
- if you have low blood salts

It is extremely important that you inform your doctor or pharmacist if you are taking or have
recently taken any other medicines, even those that are obtained without a prescription. Some
medicines may affect the way that TIKOSYN works. A list of the medicines that may affect
TIKOSYN is shown below in the section ‘Taking other medication with TIKOSYN’. However, the following medicines must never be taken during your course of TIKOSYN
treatment:

• Cimetidine (a medicine for treating stomach ulcers)
• Verapamil (a medicine for treating angina, high blood pressure or an irregular heart
  beat)
• Some medicines used to treat fungal infections, such as ketoconazole or itraconazole
• Other drugs to control your heart rhythm
• Cisapride (a medicine for stomach problems)
• Bepridil
• Medicines for the treatment of mental conditions, such as prochlorperazine
• Certain antidepressants and certain neuroleptics
• Medicines for allergies or hay fever (antihistamines)
• Certain antibiotics, such as erythromycin and trimethoprim
• Megestrol
• Medicines to treat AIDS (protease inhibitors), such as ritonavir

Take special care with TIKOSYN:

In a small number of people (less than one in a hundred), dofetilide may make the heart beat
irregularly, causing you to feel dizzy or have palpitations. If this happens, it is most likely to
occur during the first few days of treatment. This is why the doctor has monitored your heart
carefully and has made sure the medicine is working properly

If you have palpitations, or feel faint or dizzy, you must seek urgent medical advice before
taking your next TIKOSYN capsule.

If you experience prolonged diarrhoea, sweating, thirst or vomiting, you must tell your doctor
as these conditions can change the balance of salts in your body and affect the way that
TIKOSYN works.

Before you started your TIKOSYN treatment, your doctor will have worked out which dose is
right for you. If you answered ‘Yes’ to any of the following questions, your doctor may have
decided to give you a lower dose or special care:
• Have you ever had any kidney problems?
• Have you ever had any other heart problem?

You must tell your doctor if you are taking any other medicines for any reason as these may
interfere with the way TIKOSYN works.

Taking TIKOSYN with food and drink:
TIKOSYN can be taken with or without food. You should swallow the whole capsule with a glass of water.

**Pregnancy**
TIKOSYN should not be taken during pregnancy. Contact your doctor if you become pregnant while taking TIKOSYN.

**Breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines:**
TIKOSYN does not affect your ability to drive or use machines.

**Important information about some of the ingredients of TIKOSYN:**
You should not take TIKOSYN if you are allergic to the colouring agent FD&C Yellow 6 (E110).

**Taking other medicines with TIKOSYN:**
It is extremely important that you inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those that are obtained without a prescription.

Some medicines, when taken at the same time as TIKOSYN, may change the effects of TIKOSYN. Discuss with your doctor if you take or have taken any of the medicines listed below:

- Cimetidine (a medicine for treating stomach ulcers).
- Verapamil (a medicine for treating angina, high blood pressure or an irregular heart beat).
- Cisapride (a medicine for stomach problems).
- Bepridil.
- Metformin (a medicine taken to treat diabetes)
- Some medicines used to treat fungal infections, such as ketoconazole oritraconazole
- Other drugs to control your heart rhythm
- Medicines for the treatment of mental conditions such as prochlorperazine
- Some diuretics (water tablets) such as triamterene or amiloride
- Certain antidepressants and certain neuroleptics
- Medicines for allergies or hay fever (antihistamines)
- Certain antibiotics, such as erythromycin and trimethoprim.
- Megestrol
- Medicines to treat AIDS (protease inhibitors), such as ritonavir

If you go into hospital or are prescribed another medicine, you must tell your doctor that you are taking TIKOSYN.

Always carry a list of all the medicines you are taking. If you have to go to the hospital or are treated by other doctors or dentists, tell them that you are taking TIKOSYN and show them a list of the medicines you are taking. They need this information to make sure your medicines are safe to take at the same time.

3. **HOW TO TAKE TIKOSYN**

Always follow your doctor’s instructions.
The usual dose of TIKOSYN is 500 micrograms of dofetilide, taken twice daily with approximately 12 hours between each dose. It is very important that you regularly take the exact dose of TIKOSYN that your doctor has prescribed for you and that you never take an extra dose of TIKOSYN.

Lower doses (250 micrograms twice daily, 125 micrograms twice daily or 125 micrograms once daily) may be given to some people, for example those with reduced kidney function, some heart diseases or those who are sensitive to this type of medicine. When you started your treatment with TIKOSYN, your doctor will have monitored your heart and conducted some other tests. The results of these tests will have helped the doctor decide which dose of TIKOSYN is right for you. Do not change the dose for yourself.

It is important that you keep taking your medicine until your doctor tells you to stop. If you have palpitations, or feel faint or dizzy, you must seek urgent medical advice before taking your next TIKOSYN capsule. Your condition may get worse if you stop taking TIKOSYN.

**If you take more TIKOSYN than you should:**

If you take more capsules than prescribed, or if someone else takes your capsules, you must seek urgent medical advice or go to the nearest hospital casualty department immediately. Take your packet of TIKOSYN with you.
If you forget to take TIKOSYN:

It is important that you take your TIKOSYN capsules regularly. If you forget to take one capsule, take your next dose when it is due but never take a double dose to make up for the forgotten dose. If you forget to take more than one dose, contact your doctor before continuing your treatment.

4. POSSIBLE SIDE EFFECTS

Like all medicines, TIKOSYN can have side effects. Very rarely, TIKOSYN itself may cause rhythm disturbances of the heart (see section ‘Take special care with TIKOSYN’). You should contact your doctor urgently if you experience dizziness, palpitations or worsening of your symptoms. Other side effects may include weakness, headache, nausea, dizziness and breathlessness. Very rarely, cases of low blood platelet count and mild changes in liver function may occur. If you experience any of these side effects and they cause you concern, you should see your doctor.
If you notice any other unwanted effects not mentioned in this leaflet, please tell your doctor or pharmacist.

5. STORING TIKOSYN

Keep out of the reach and sight of children
Do not store above 30°C
Do not use after the expiry date stated on the carton

This leaflet was last approved on {date}
**Further information**
For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

<table>
<thead>
<tr>
<th>Country</th>
<th>Address</th>
<th>Contact Details</th>
</tr>
</thead>
</table>
| Belgique / België / Belgien | Pfizer S.A.  
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| Deutschland   | Pfizer GmbH  
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Lars Sonckin kaari 4  
FI-02600 Espoo | +358 (0)9 43 00 40 |
| Sverige       | Pfizer AB  
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SE-183 25 TÄBY | +46 (0)8 519 062 00 |
| United Kingdom | Pfizer Limited  
Ramsgate Rd  
Sandwich, Kent GB-CT13 9NJ | +44 (0)1304 61 61 61 |
TIKOSYN 500 microgram hard capsules
(dofetilide)

- The active substance is dofetilide
- The other ingredients are: microcrystalline cellulose, maize starch, colloidal anhydrous silica, magnesium stearate, gelatin, titanium dioxide (E171), FD&C Yellow 6 (E110), black ink containing black iron oxide (E172), shellac, soya lecithin and anti-foam DC 1510

The licence to market TIKOSYN is held by:
Pfizer Limited, Sandwich, Kent, CT13 9NJ, UK.

TIKOSYN is made by:
Pfizer S.A., Zone Industrielle de Pocé-sur-Cisse, 37401 Amboise Cedex, France.

1. **WHAT TIKOSYN IS AND WHAT IT IS USED FOR**

TIKOSYN is presented as hard capsules containing 500 micrograms of dofetilide per capsule. TIKOSYN belongs to a group of medicines called antiarrhythmics. These medicines are used to control an irregular or rapid heartbeat.

TIKOSYN is taken to control the rhythm of the heart. It is used in people whose hearts beat irregularly or too fast. These conditions are called arrhythmias. An abnormal heartbeat reduces the ability of the heart to pump blood around the body. This condition may cause palpitations or an uncomfortable feeling in the chest, breathlessness, tiredness, dizziness, faintness, and anxiety. TIKOSYN relieves symptoms by helping the heart to beat normally.

TIKOSYN has been prescribed for you. Do not allow anyone else to take it.

2. **BEFORE YOU TAKE TIKOSYN**

**Do not take TIKOSYN:**
- if you are hypersensitive (allergic) to dofetilide or any of the other ingredients of TIKOSYN, in particular FD&C Yellow 6 (E110).
- if you have one of the following heart conditions: congenital or acquired long QT syndrome, sick sinus syndrome or heart block without a pacemaker.
- if you have severe liver or kidney disease or are on kidney dialysis
- if you have a slow heartbeat
- if you are under the age of 18
- if you have low blood salts

It is extremely important that you inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those that are obtained without a prescription. Some medicines may affect the way that TIKOSYN works. A list of the medicines that may affect TIKOSYN is shown below in the section ‘Taking other medication with TIKOSYN’. However, the following medicines must never be taken during your course of TIKOSYN treatment:

- Cimetidine (a medicine for treating stomach ulcers)
- Verapamil (a medicine for treating angina, high blood pressure or an irregular heart beat)
- Some medicines used to treat fungal infections, such as ketoconazole or itraconazole
- Other drugs to control your heart rhythm
- Cisapride (a medicine for stomach problems)
- Bepridil
- Medicines for the treatment of mental conditions, such as prochlorperazine
- Certain antidepressants and certain neuroleptics
- Medicines for allergies or hay fever (antihistamines)
- Certain antibiotics, such as erythromycin and trimethoprim
- Megestrol
- Medicines to treat AIDS (protease inhibitors), such as ritonavir

Take special care with TIKOSYN:

In a small number of people (less than one in a hundred), dofetilide may make the heart beat irregularly, causing you to feel dizzy or have palpitations. If this happens, it is most likely to occur during the first few days of treatment. This is why the doctor has monitored your heart carefully and has made sure the medicine is working properly

If you have palpitations, or feel faint or dizzy, you must seek urgent medical advice before taking your next TIKOSYN capsule.

If you experience prolonged diarrhoea, sweating, thirst or vomiting, you must tell your doctor as these conditions can change the balance of salts in your body and affect the way that TIKOSYN works.

Before you started your TIKOSYN treatment, your doctor will have worked out which dose is right for you. If you answered ‘Yes’ to any of the following questions, your doctor may have decided to give you a lower dose or special care:

- Have you ever had any kidney problems?
- Have you ever had any other heart problem?

You must tell your doctor if you are taking any other medicines for any reason as these may interfere with the way TIKOSYN works.

Taking TIKOSYN with food and drink:

TIKOSYN can be taken with or without food. You should swallow the whole capsule with a glass of water.
Pregnancy
TIKOSYN should not be taken during pregnancy. Contact your doctor if you become pregnant while taking TIKOSYN.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines:
TIKOSYN does not affect your ability to drive or use machines.

Important information about some of the ingredients of TIKOSYN:
You should not take TIKOSYN if you are allergic to the colouring agent FD&C Yellow 6 (E110).

Taking other medicines with TIKOSYN:
It is extremely important that you inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those that are obtained without a prescription.

Some medicines, when taken at the same time as TIKOSYN, may change the effects of TIKOSYN. Discuss with your doctor if you take or have taken any of the medicines listed below:
- Cimetidine (a medicine for treating stomach ulcers).
- Verapamil (a medicine for treating angina, high blood pressure or an irregular heart beat).
- Cisapride (a medicine for stomach problems).
- Bepridil.
- Metformin (a medicine taken to treat diabetes)
- Some medicines used to treat fungal infections, such as ketoconazole or itraconazole
- Other drugs to control your heart rhythm
- Medicines for the treatment of mental conditions such as prochlorperazine
- Some diuretics (water tablets) such as triamterene or amiloride
- Certain antidepressants and certain neuroleptics
- Medicines for allergies or hay fever (antihistamines)
- Certain antibiotics, such as erythromycin and trimethoprim.
- Megestrol
- Medicines to treat AIDS (protease inhibitors), such as ritonavir

If you go into hospital or are prescribed another medicine, you must tell your doctor that you are taking TIKOSYN.

Always carry a list of all the medicines you are taking. If you have to go to the hospital or are treated by other doctors or dentists, tell them that you are taking TIKOSYN and show them a list of the medicines you are taking. They need this information to make sure your medicines are safe to take at the same time.

3. HOW TO TAKE TIKOSYN

Always follow your doctor’s instructions.

The usual dose of TIKOSYN is 500 micrograms of dofetilide, taken twice daily with approximately 12 hours between each dose. It is very important that you regularly take the
exact dose of TIKOSYN that your doctor has prescribed for you and that you never take an extra dose of TIKOSYN.

Lower doses (250 micrograms twice daily, 125 micrograms twice daily or 125 micrograms once daily) may be given to some people, for example those with reduced kidney function, some heart diseases or those who are sensitive to this type of medicine. When you started your treatment with TIKOSYN, your doctor will have monitored your heart and conducted some other tests. The results of these tests will have helped the doctor decide which dose of TIKOSYN is right for you. Do not change the dose for yourself.

It is important that you keep taking your medicine until your doctor tells you to stop. If you have palpitations, or feel faint or dizzy, you must seek urgent medical advice before taking your next TIKOSYN capsule. Your condition may get worse if you stop taking TIKOSYN.

If you take more TIKOSYN than you should:

If you take more capsules than prescribed, or if someone else takes your capsules, you must seek urgent medical advice or go to the nearest hospital casualty department immediately. Take your packet of TIKOSYN with you.

If you forget to take TIKOSYN:

It is important that you take your TIKOSYN capsules regularly. If you forget to take one capsule, take your next dose when it is due but never take a double dose to make up for the forgotten dose. If you forget to take more than one dose, contact your doctor before continuing your treatment.

4. POSSIBLE SIDE EFFECTS

Like all medicines, TIKOSYN can have side effects. Very rarely, TIKOSYN itself may cause rhythm disturbances of the heart (see section ‘Take special care with TIKOSYN’). You should contact your doctor urgently if you experience dizziness, palpitations or worsening of your symptoms. Other side effects may include weakness, headache, nausea, dizziness and breathlessness. Very rarely, cases of low blood platelet count and mild changes in liver function may occur. If you experience any of these side effects and they cause you concern, you should see your doctor.

If you notice any other unwanted effects not mentioned in this leaflet, please tell your doctor or pharmacist.

5. STORING TIKOSYN

Keep out of the reach and sight of children
Do not store above 30°C
Do not use after the expiry date stated on the carton

This leaflet was last approved on {date}
**Further information**
For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

<table>
<thead>
<tr>
<th>Country / Region</th>
<th>Address</th>
<th>Phone Numbers</th>
</tr>
</thead>
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