strong evidence suggesting that women treated with dofetilide for SVA may have higher rate of sudden and unexpected cardiac deaths (SUCD). There is no other gender related safety issue except that oral contraceptives (OC) and possibly, hormone replacement therapy (HRT), may have clinically important interactions with dofetilide (see Clinical Pharmacology).

cc:
NDA 20-931
HFD-110
HFD-110/Proj Manager
HFD-110/SChen

JAN 26 1999

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CDER/ODE-I/DIV CARDIO-RENAL DRUGS PRODUCTS

Date: January 19, 1999
From: Shaw T. Chen, M.D., Ph.D., Medical Group Leader, HFD-110
Through: Director, Division of Cardiorenal Drug Products, HFD-110
To: Director, Office of Drug Evaluation I, HFD-100
SUBJECT: NDA 20-931
Tykosyn (dofetilide) for Supraventricular Arrhythmias (SVA), Approvability

OVERVIEW

This memorandum and the attached material constitute the Team Leader's recommendation that NDA 20-931, Tykosyn (dofetilide capsules), be approved for acute conversion of atrial fibrillation/flutter (AF/AFl). For oral treatment of chronic SVA to maintain normal sinus rhythm, the drug should be used only in patients with AF/AFl *and* left ventricular dysfunction. The relative risk/benefit of dofetilide is less clear in uncomplicated AF/AFl. Dofetilide has not been shown to be effective in preventing attacks of paroxysmal SVA, either tachycardia (pSVT) or fibrillation/flutter (pAF/pAFl).

This package is being transmitted with reviews by all relevant disciplines. The primary medical reviews were conducted jointly by Drs. Knudsen (clinical pharmacology), Ganley (efficacy), Gordon (safety, pharmacodynamics), Williams (DIAMOND trials), Hung (statistics, efficacy) and Cui (statistics, DIAMOND trials). This memorandum was synthesized from their findings and their individual reports are attached. In addition, comments by Dr. Fadiran on biopharmaceutic issues and by Dr. Gill-Kumar on pharmacology were also summarized. As of the date of this memo, all of the above reviews have been completed. There are no major, unresolved issues which may affect the action recommended.

Dofetilide is a new Class III antiarrhythmic structurally similar to sotalol, it delays cardiac repolarization through inhibition of potassium channel and I_{kr} current. The sponsor claims that dofetilide "selectively" prolongs the effective refractory period and this selectivity is presumably the basis of anti-arrhythmic activities without much of the undesirable properties associated with other current therapies. However, there is little comparative evidence to support this contention. Instead, the pro-arrhythmic potential of dofetilide remains as a serious concern and the results of mortality trials in congestive heart failure have not provided enough assurance about its safety in patients with uncomplicated atrial arrhythmia. While dofetilide is more effective than placebo in maintaining normal sinus rhythm, the perceived patient benefits of such use may not be adequate to justify a non-trivial proarrhythmic risk, especially with the chronic oral maintenance therapy. On the other hand, the risk of short-term, closely monitored use in converting atrial arrhythmias acutely is probably more acceptable and although its absolute effectiveness in such setting is not very high, it is certainly more efficacious than placebo.

The total safety database consists of more than 9,000 subjects in all studies and nearly half (4,259) of whom received oral dofetilide. Data from the first Safety Update are included; no further update is necessary before the recommended regulatory action. This application will be discussed at the next Cardiorenal Advisory Committee meeting on January 28 of 1999.

Inspection of the clinical trials has been completed in 4 of the 5 sites scheduled for auditing. The finding so far does not affect the overall integrity of the data.

PRECLINICAL EVALUATIONS

Chemistry

The sponsor has addressed all the deficiencies in chemistry, manufacturing and analytical controls (see related reviews) and that part of the application is considered approvable. Final inspection of the facilities has been completed except for one late-submitted site.

Preclinical Pharmacology

Dofetilide has been adequately characterized with respect to its preclinical pharmacokinetics and pharmacodynamic properties. The extent of exposure, in dose and duration, to dofetilide in animals toxicology studies was adequate for safety margin assessment. Dofetilide causes testicular atrophy in three animal species, but it occurred only at high doses, had adequate margin from no-effect dose and did not affect fertility in rats (see summary of pharmacology review). The sponsor has been asked to repeat a human lymphocytes test and a mouse bone marrow study, but the soon-to-be-submitted results are only to provide minor labeling details in "genotoxicity and clastogenicity" and do not affect approvability. There are no other clinically relevant issues in animal toxicity. Labeling changes from the sponsor's proposal as recommended in the pharmacology review are acceptable and will be incorporated in the marked-up draft.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Pharmacokinetic profile of dofetilide has been described in detail in the biopharmaceutical reviews by Dr. Fadiran, and all kinetic parameters are referred to his report. A few issues which are more directly relevant to efficacy and safety, as well as the instruction for clinical use, are summarized and commented as follows:

1. Dofetilide is highly **bioavailable** (absolute bioavailability >90%) with a low intra- and inter-personal variability in plasma concentrations; its pharmacokinetics are nearly linear with single and multiple dosing. At the proposed dose of 500 mcg bid, steady state (reached in 3-5 days) T_{max} is about 2 hrs and the terminal $T_{1/2}$ of approximately 8-10 hrs. Dofetilide does not accumulate with once daily dosing, but does so at an index of 1.5-2 with bid administration. Plasma protein binding is about 60-70% and independent of concentration or renal function. Detectable metabolites are mostly inactive (>20 x less than dofetilide).
2. Orally administered dofetilide is 50-75% cleared by renal route and the apparent plasma **clearance** for dofetilide (CL/f) was proportional to the creatinine clearance (CLCr), which can be described by the following equation:

   CL/f=2.81+0.17 x CLCr

   (r^2 = 0.88, see Dr. Fadiran's review)

   To prevent over-exposure in patients with renal impairment, the sponsor has proposed that dose be reduced sequentially in half for CLCr of 40-60 ml/min and 20-40 ml/min (see Dosing Information below). Similar dependence of dofetilide clearance on renal function was also observed in the DIAMOND studies (see below in Safety for description of the

trials); dofetilide clearance was about 40% and 60% lower for the mildly (CLCr 40-60 ml/min) and the moderately (CLCr 20-40 ml/min) impaired (Dr. Fadiran's review).

3. The clearance of dofetilide is not affected by moderate **hepatic** dysfunction, thus dose adjustment does not appear necessary. However, as noted below in Safety, there was a mild increase in QT intervals for the moderately impaired and the kinetics in patients with severe dysfunction have not been studied. After adjusting for creatinine clearance, there is no correlation between dofetilide clearance and ischemic heart disease, left ventricular function or the presence of SVA.
4. Lower dofetilide clearance in the **elderly** (64-73 yrs) was mainly due to reduced creatinine clearance in the aged group. Effects of **race** on pharmacokinetics of dofetilide have not been studied. Body weight accounts for some, but not all, of the **gender** difference in pharmacokinetics of dofetilide. Population kinetics indicated a 12-18% lower CL/f in female subjects, resulted in 20% and 10-15% higher C_{max} and AUC, respectively. Other data suggested that this gender difference may be exacerbated when dofetilide is co-administered with certain drugs (see below).
5. Dofetilide is metabolized by the **CYP450** (mostly **3A4**) system, it does not inhibit significantly metabolism of other substrates for 3A4, 2C9 or 2D6 at concentrations up to 100 μM (therapeutic concentration in the nM range).
6. The following **interactions** between dofetilide and some commonly used drugs may be of clinical importance (dofetilide was dosed at 500 mcg bid unless noted otherwise):

X	X's effect on Dofetilide's Cmax	AUC
cimetidine 400 mg bid	+52%	+58%
verapamil 80 mg tid	+42%	+14%
oral contraceptive#	+100%	
ketoconazole 400 mg qd	+74%	+58%

dofetilide 750 mcg bid, see following text for other details

It was hoped that the data in the above table would have defined the extent of increase in dofetilide exposure due to potential interactions with other P450 substrates, ranged from a weak inhibitor (verapamil) to one of the strongest (ketoconazole). However, the ketoconazole's effect on dofetilide clearance does not solely involve the cytochrome system (see table below), thus it is not sure whether other strong inhibitor of the same enzyme system, without any renal component, may result in even higher exposure to dofetilide.

ketoconazole's effect on Dofetilide's	renal clearance	non-renal clearance
female	-35%	-55%
male	-31%	-26%

The ketoconazole study also re-enforced that concern that exposure to dofetilide in female patients may be highly labile to drug interaction:

changes in Dofetilide's	Cmax	AUC
female	+97%	+77%
male	+53%	+41%

As noted by both Drs. Fadiran and Gordon, since the oral contraceptive (OC) study was not intended to measure the changes in dofetilide kinetics (instead to assess the effect of dofetilide on OC), the data should be viewed with reservation. The reviewers also pointed out that the OC was not dosed concomitantly with dofetilide (2 hrs later), thus the interaction may be underestimated. The sponsor is currently conducting another study looking at the interaction with hormone replacement therapy (HRT).

7. Other drug interaction studies (mostly normal subjects) showed that:
dofetilide does not affect the kinetics of:
warfarin, digoxin, propranolol, phenytoin, theophylline and oral contraceptives,
and the following drugs do not affect the kinetics of dofetilide:
amlodipine, phenytoin, glyburide, ranitidine, omeprazole, antacids and theophylline.

Since there is a tight relationship between dofetilide concentration and degree of drug-induced QT prolongation (see below in pharmacodynamics), the above comments on pharmacokinetics must be taken seriously.

Pharmacodynamics

As summarized in the pharmacodynamic review by Dr. Gordon, dofetilide blocks the potassium channel and I_{kr} current, increases duration and refractoriness of cardiac action potential. These effects are reflected by prolongation of QT/QT_c intervals and a propensity to proarrhythmic events.

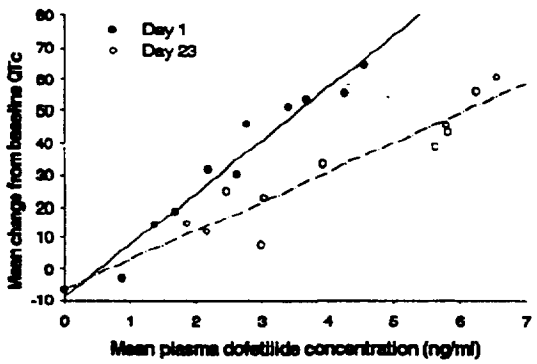
Dofetilide prolongs the monophasic action potential and increases effective refractory periods in the atria, ventricle, AV node and His-Purkinje system. It does not change sinus node recovery times or conduction velocities within atria, from AV node to His and from His to ventricle. Results in patients with or without conduction abnormality and /or sinus node dysfunction were similar. The increases in QT intervals were significantly and consistently dose-related, reached maximum in about 2 hrs and returned to baseline at 12 hrs. Dofetilide has no effect on the QT dispersion and does not change PR interval or QRS duration. Defibrillation threshold was not affected by dofetilide.

Dofetilide lowers heart rate slightly (by 6 bpm), but does not change blood pressure appreciably. Few other hemodynamic parameters measured in 3 invasive studies were affected by dofetilide treatment. Most importantly, there is no evidence that dofetilide has any negative inotropic effect on the myocardium. For patients who were maintained on normal sinus rhythm (NSR) with dofetilide, exercise tolerance was improved in patients with history of chronic AF/AFl. But the number of patients was too small (56 total in Study 120X, see Efficacy below for details) and the phenomenon was not seen in another study (Study 313).

Pharmaco-kinetics/-dynamics (PK/PD) Correlation & Population Studies

In normal subjects, there is a linear relationship between plasma concentration of dofetilide and QT_c prolongation (see graph on the next page). This pharmacodynamic parameter is quite sensitive to the change in plasma concentration and such sensitivity decreases slightly at steady state from that with initial dosing. As shown on the plots on the next page, the slope is 15-25 ms/(ng/mL) for Day 1 and 10-15 ms/(ng/mL) on Day 23. Since the C_{max} for a 500 mcg bid dose is around 2-3 ng/mL, a 50% increase in plasma concentration (e.g., by drug interaction) will

increase QT_c by 20-30 ms at the initial dosing. A similar kinetics/dynamics relationship (slope of 11 ms/(ng/mL)) was observed in a population PK/PD study of Phase II studies.



Since there is almost no hysteresis in QT_c changes vs plasma concentration with oral dosing of dofetilide, QT_c prolongation in downward titration of the doses (as recommended, see below in Dosing Information) should follow the above relationship (see Fig. 6 of Dr. Fadiran's review). This PK/PD correlation is not affected by age, gender or renal function.

Population PK/PD analyses of Phase II studies generated a pharmacokinetic profile of dofetilide similar to that described above and confirmed that creatinine and gender are the most important covariates for apparent clearance of dofetilide. The population studies also showed that dofetilide has predictable, linear pharmacokinetics with low inter-individual and residual variabilities. A separate population studies using a larger database of Phase III trials showed essentially the same results in pharmacokinetics. In addition, the Phase III PK/PD studies further correlated certain adverse experiences and efficacy measures with kinetic parameters (C_{max} and AUC). A great majority of proarrhythmia episodes (TdP) occurred at AUCs > 60 $ng.ml^{-1}.h$ (prevalence of >2.9% vs < 1% for lower AUC, TdP also increases with C_{max}). Following the recommended dose adjustment for creatinine clearance reduced incidence of proarrhythmia in patients with renal impairment. Responses to dofetilide (remaining in NSR) in patients with paroxysmal SVA were also associated with higher AUC's (> 60 $ng.ml^{-1}.h$, see Dr. Fadiran's review).

Other Biopharmaceutical Issues

The to-be-marketed formulation has been shown to be bioequivalent to the clinical trial version. Although the biopharmaceutical reviewer is not yet completely satisfied with the dissolution specification (see Dr. Fadiran's review), the issue can be resolved post-approval.

MAJOR TRIALS SUPPORTING EFFICACY

Major supports of efficacy for dofetilide in atrial arrhythmia were derived from the following two multicenter, randomized, double-blind, parallel group and placebo controlled trials, involving a total of 996 patients with AF/AFl*.

Study **115-345**	671 patients	acute conversion/maintenance, 125, 250, 500 mcg
Study **115-120**	325 patients	(similar design, US study)

The atrial arrhythmias, mostly fibrillation, evaluated in these trials were of relatively recent onset in Study 120 (diagnosed within 2 wks to 6 months), but may be more chronic in Study 345 (up to 2 years). Substantial number of patients had history of structural heart diseases (about 67% in Study 120, 47% in Study 345, Table 3.2 NDA Section 2.H.4.A.1), but most were stable hemodynamically, adequately anti-coagulated, and more than half may be asymptomatic (60-70% in Study 120, >50% in Study 345 [defined in the latter as in NYHA Class I]).

In both studies, the study drugs were started at the randomized dose then reduced (Study 120) or discontinued (Study 345) for QT prolongation during the conversion phase and adjusted for creatinine clearance (both studies, but implemented at different time after the study started, see Primary Efficacy Review**) to avoid excessive exposure. The efficacy analysis for acute conversion (a secondary endpoint) was based on the percentages of patients whose arrhythmias were converted to normal sinus rhythm (NSR) and maintained for 24 hrs. For chronic maintenance treatment, the endpoint event was recurrence of AF/AFl lasting >24 hrs and the **primary efficacy** measures were the **proportions of patients remained in sinus rhythm at 6, 9, 12** (Study 120) or **at 12 months** (Study 345) of double blind therapies (Kaplan-Meier curves). For Study 120, the pre-specified intent-to-treat analysis included all randomized patients, but for Study 345, only those who were converted to NSR during the acute phase were specified.

In either protocol, there was no serious effort to collect and analyze data on symptom improvement (patient questionnaires in Study 120 and quality of life in Study 345). These measures were either one of the many secondary endpoints or not defined in details prospectively, and the reviewers were reluctant to place any significance on these findings (see Primary Efficacy Review). In a substudy on exercise tolerance (**120X**), not much can be concluded from an unadjusted analysis of a small sample (see below). Other chronic AF/AFl studies (Studies **311, 320**), although apparently positive, were too small (10-20/group).

The sponsor also presented positive results of a six-month, 80-patient study on paroxysmal supraventricular tachycardia (**pSVT**, Study **372**, see below). The design was similar to those of AF/AFl studies with primary endpoint of time to first recurrence of symptomatic pVST attack. Results of the other larger pSVT study (300 patients, Study **119**) were not significant, probably because of subtherapeutic doses (see Primary Efficacy Review). It is clear, although somewhat puzzling, that dofetilide is not effective for other types of paroxysmal SVAs (pAF/AFl), or ventricular arrhythmias (VA) (see list of studies in NDA and Primary Efficacy Review). A mortality study in patients with heart failure or post myocardial infarction (the DIAMOND Study), while provides no support for the efficacy claims, is needed for safety considerations (see below).

* Study 345 is an European study. For other differences in the two protocols, see primary review.

** The joint medical/statistical review on efficacy by Drs. Ganley/Hung.

EFFICACY FINDINGS OF THE MAJOR TRIALS

Maintenance of Normal Sinus Rhythm

Statistically, **Study 345** was positive with quite impressive finding on the primary endpoint analysis. The probability of remaining in NSR was significantly higher for dofetilide-treated patients than for those on placebo* (from Tables 345.4 of Primary Efficacy Review**):

Probability of Remaining in NSR (converted, Study 345)

dofetilide (bid)	125 mcg	250 mcg	500 mcg	placebo
3 months	0.56	0.58	0.74	0.34
6 months	0.50	0.56	0.71	0.26
9 months	0.39	0.53	0.67	0.22
12 months	0.39	0.51	0.66	0.21
p vs placebo	0.0059	0.0001	0.0001	

While only patients who were successfully converted to NSR (the "Maintenance Population" or referred to as the "Converted Group" in this memo) are included in this specified primary analysis of Study 345, and thus not a true "intent-to-treat", the reviewers agree that this is appropriate and more clinically relevant (see Primary Efficacy Review). Analyses including non-converted patients did not change the overall study outcome (Table 345.5). Dr. Hung also performed two additional analyses to account for the differences in censoring time (Tables 345.6, 345.7) and speculated on the "worst case scenario" in such adjustments. For Study 345, all these additional analyses demonstrate superiority of dofetilide over placebo (except the "worst scenario" case for the lowest 125 mcg dose) and attest to the robustness of the findings (Tables 345.8, 345.9).

Results of the second study (**Study 120**) also showed that, over the same period of treatment for 12 months, dofetilide is more effective than placebo in maintaining NSR:

Probability of Remaining in NSR (All randomized***, Study 120, Table 120.12)

dofetilide (bid)	125 mcg	250 mcg	500 mcg	placebo	p vs placebo
12 months	0.29	0.28	0.47	0.20	0.0345

However, it should be noted that the 12 month result was only part of the pre-specified primary analysis**** and the p-values were not adjusted for multiple comparisons. Treatment effects at other time points trended in the right direction, but did not quite make it statistically:

Probability of Remaining in NSR (All randomized, Study 120, Table 120.12)

dofetilide (bid)	125 mcg	250 mcg	500 mcg	placebo	p vs placebo
6 months	0.32	0.37	0.50	0.30	0.1250
9 months	0.31	0.34	0.48	0.23	0.0586

* Log rank test used for all analyses.

** All table numbers of source efficacy data in this memo refer to those in the Primary Efficacy Review, unless noted otherwise.

*** Unlike Study 345, "all-randomized" or "intent-to-treat" was the specified primary analysis for Study 120.

**** The analyses at 6,9,12 months were specified as primary, but the study was powered for the 6 month effect.

On the other hand, for patients who were at first *successfully converted*, a more clinically relevant measure used as the primary analysis in Study 345, dofetilide was clearly more effective*:

Probability of Remaining in NSR (Converted group, Study 120, Table 120.12.b)

dofetilide (bid)	125 mcg	250 mcg	500 mcg	placebo	p vs placebo
6 months	0.44	0.50	0.62	0.37	0.0619
9 months	0.42	0.46	0.60	0.28	0.0161
12 months	0.40	0.37	0.58	0.25	0.0105

This is especially true for the 500mcg dose:

Incidence of relapse (Converted group, Study 120, Table 120.15a):

Incidence	500 mcg bid	placebo	p vs placebo
6 months	34.4%	61.8%	0.014
9 months	36.1%	69.1%	0.002
12 months	37.7%	72.1%	0.001

The 500 mcg dose was also better than placebo in all-randomized patients, with nominal p ranged from 0.051 at 6 months to 0.014 at 9 months and 0.008 at 12 months (Table 120.15). In Study 120, adjustment for differences in censoring time reduced the statistical significance in general (see Dr. Hung's analyses in Primary Efficacy Review), but the data still suggested a benefit for the 500 mcg dose, especially after 6 months (Tables 120.15 and 120.15a).

For maintenance therapy in both Studies 345 and 120, the treatment effects are also evident visually in the presentation of **Kaplan-Meier curves**, which were well-separated for different treatment groups by 3 months (see Primary Efficacy Review).

Maintenance of NSR by dofetilide, at a higher dose range, was also tested in two additional smaller studies (**Studies 311, 320**), but they were not powered enough to show statistical significance of the treatment effect. The results were not contradictory to those of the definitive trials and appeared to be supportive (Table 311.3 of Primary Efficacy Review and summary in NDA Section H.5.B.1):

Proportion of patients in NSR at 3 months (dose in bid)

Studies	250 mcg	500 mcg	750 mcg	placebo
311	10/21	13/21	12/21	7/20
320#	-	9/10	9/9	4/9

terminated prematurely for safety of 750 mcg dose.

Dofetilide is probably also effective in maintaining NSR for AF/AFl patients with more significant cardiovascular morbidity as in the **DIAMOND** trials (506 patients had AF/AFl at baseline). Although the subset was not truly randomized, dofetilide treated patients were more likely to stay in NSR at the end of 12 months (47% vs 14% on placebo, non-converted counted as relapsed on Day 1, Amendment of 12/3/98).

* For all non-primary endpoints/analyses, p-values are only nominal and not adjusted for multiple comparisons.

Acute Conversion to NSR

For acute conversion to NSR, a secondary endpoint in both major studies, dofetilide was consistently more effective than placebo at nearly all doses, although the overall conversion rates were low and most patients required cardioversion to restore the NSR (see also Tables 19 & 20 of NDA, Section 2.H.4.C).

Conversion to NSR by dofetilide (Tables 120.22, 345.13):

Studies	125 mcg	250 mcg	500 mcg	placebo
345	6.0%	10.5%	29.5%	1.5%
p vs placebo	0.037	0.001	0.001	
120	6.1%	9.8%	29.9%	1.2%
p vs placebo	0.098	0.015	< 0.001	

Success rates of cardioversion ranged 70-90% and were not affected by treatment with dofetilide or the dosage in the two studies.

Symptomatic Improvement

As noted above, clinical benefit of dofetilide treatment, other than rhythm control, has not been a primary objective in the dofetilide development program. In the **exercise substudy** (120X, see Sponsor's summary report in Section 2.H.4.B.1 of NDA, pages 15-16), the change in exercise time was analyzed for only a very small subset of patients and the "favorable" conclusion has been hinged on the comparisons between baseline and measurements after 60 days of therapy. None of between-group analyses showed an effect, even before adjustment for multiple endpoints. An average improvement in exercise time of 23.8±9.8% from baseline in 21 patients who remained in NSR was compared with 4.6±16.7% increase in another 13 patients who relapsed (p=0.2, Table 6.20 of NDA). An even smaller subset was used for comparison between 500 mcg dose group (9) and placebo (7); showing a treatment effect of 59±28.3% improvement from baseline (over 2.5±8.9% for placebo, p=0.08, Table 6.21.1 of NDA) for dofetilide. In view of the non-significant primary outcome, issues of multiple analyses, as well as the extremely small sample size and high variability in exercise time, the substudy finding is hardly convincing or conclusive.

Using a standardized grading scale, the sponsor also claimed that overall severity and frequency of **arrhythmia-associated symptoms** were reduced in patients remained in NSR, as compared with those who relapsed (Study 120, Table 120.19). However, when maintained and relapsed patients were grouped together in between-treatment comparison (500 mcg bid vs placebo), the difference was not significant (ibid). A few specific symptoms were probably improved by dofetilide (e.g. palpitation, shortness of breath and worry, see Table 120.21). Some of several (total of 5 or more) different quality-of-life scales used in Study 345 also showed an improvement for patients who remained in NSR, (vs those who relapsed, NDA Section 2.H.4.B.1, pages 16-17). Most , if not all, of the difficulties in the interpretation of exercise data, as noted above, also apply here for the symptomatic improvement.

Dofetilide treatment appeared to improve some echocardiogram parameters (NDA Section H.4.B.1, Tables 10.1-10.3), but such findings are without statistical significance (of many secondary endpoints) and of little clinical meaning (unaccepted surrogate endpoints).

Subgroup Analyses

For efficacy, there is no surprising finding in subgroup analyses with respect to **age** and **gender**. Both demographic subpopulations had similar response to dofetilide treatment, either in all randomized patients or in those who were successfully converted (NDA Section 2.H.4.B.1, pages 11-12). Minority **racial groups** were not adequately represented in the dofetilide studies to allow any definite conclusion (also Tables 120.16 & 345.12 of Primary Efficacy Review).

Comparing with other Antiarrhythmics

Without a formal statistical test, dofetilide at 250-500 mcg bid appeared to be more effective than sotalol (80 mg bid) in acute conversion of chronic AF/AFl in Study 345, but only slightly better as a maintenance therapy (from Tables 345.4 & 345.13):

Study 345	dofetilide 0.25mg bid	dofetilide 0.5mg bid	sotalol 80 mg bid
acute conversion#	11%	29%	5%
maintenance##	0.51	0.66	0.49

\# % converted to NSR

\## probability of remaining in NSR at 12 months

Dofetilide has been compared with other agents, but not in chronic AF/AFl. It (at 500 mcg bid) could not be distinguished from propafenone (150 mg tid) in pSVT (Study 372), nor (at 250 mcg bid) with quinidine (300 mg bid) in pAF/pAFl (Study 363). The remaining comparisons with active controls (amiodarone, procainamide) were all in studies of ventricular arrhythmias (VA).

Effects on Paroxysmal SVT/SVA

In a study on pSVT (**Study 115-372**), dofetilide at 500 mcg bid prevented recurrent attacks of pSVT in 122 patients (Table 372.4a):

Probability of remaining attack-free (Study 372, steady state)

dofetilide (bid)	500 mcg bid	placebo
4 weeks	0.76	0.40
12 weeks	0.66	0.20
26 weeks	0.55	0.08
p vs placebo	< 0.001	

The reviewers noted that the efficacy analysis was based on data collected after 72 hrs of treatment (Steady State analysis), but there is no difference in the outcome if events from the first dose were included (First Dose analysis, Table 372.4b). As also noted in the Primary Efficacy Review, the above treatment effect may be overestimated because patients withdrawn prematurely were censored, not counted as a relapse. However, if those censored were recounted as failure, then the probability is 37.5%, which is still distinguishable from that of placebo.

While the favorable outcome of Study 372 was quite significant, the finding has not been confirmed in other pSVT or pSVA studies. Dofetilide could not be differentiated from placebo in another study (**Study 119**, 316 patients total), a study using lower dosages (<500 mcg bid) and

in a more heterogeneous population (only 18% with pSVT, the rest with pAF/pAFl).

Probability of remaining attack-free (Study 119, Table 119.8)

dofetilide (bid)	250 mcg	375 mcg	placebo
26 weeks	0.27	0.42	0.30
p vs placebo	0.544	0.211	

For treatment of paroxysmal atrial arrhythmias (pAF/pAFl), none of the additional studies (Studies 128, 363, 365, Study 114 was too small and not analyzed) showed even a marginal effect for dofetilide ($p > 0.7$ vs placebo). The failure cannot be attributed to dosage or size of the studies:

Numbers of Patients Randomized

Studies	250 mcg	500 mcg	placebo
128	-	132	129
363	48	-	50
365	-	181	89

INTERPRETATIONS OF THE EFFICACY FINDINGS

Chronic Atrial Fibrillation/Flutter

For **acute conversion** of AF/AFl to NSR, dofetilide at doses 250-500 mcg bid appeared to be more effective than placebo, although the endpoint is secondary in both Studies 345 and 120, and the statistical significance may be questionable for the one which did not quite make it for the pre-specified primary endpoint (Study 120, for maintenance of NSR). It is somewhat disappointing that the absolute success rate of acute conversion by dofetilide was less than 30% and most patients entered (and responded to) the chronic therapy were converted non-pharmacologically. Thus, while it is approvable regulatory-wise, how useful dofetilide is in acute conversion in a real clinical setting is not clear (especially comparing with ibutilide).

As an oral therapy to **maintain NSR** for chronic AF/AFl, the overall efficacy data do support the claim. While the outcome of the second study (Study 120) did only reach statistical significance for part of the primary endpoint (at 12 months, before adjusting for multiple comparison), analyses more equivalent to that specified in Study 345 (the "Converted Group", and 500 mcg vs placebo) are all consistently in favor of dofetilide with small nominal p values. Thus the evidence from Study 120 may be considered only slightly weaker than one positive trial. On the other hand, the results of Study 345 are highly significant with p values reaching 0.0001 (primary analyses for 250-500 mcg bid), thus the study by itself is probably stronger than a single conventionally positive trial ($p < 0.05$). Combining the two studies and viewed in totality, the medical reviewers are convinced that the data can be considered as equivalent to two positive trials and the efficacy of dofetilide in maintaining NSR for chronic AF/AFl has been reasonably established.

Based on the high percentage of patients who were not converted by dofetilide in the acute phase but still responded to maintenance therapy, pharmacological conversion of AF/AFl is not a prerequisite for successful long-term oral treatment. Responses in demographic/disease subgroups were in general similar to that of overall patient population and there is no need to differentiate the

use in them, including those with more severe cardiovascular morbidity (as in DIAMOND Study, not on the basis of efficacy but maybe for safety, see below). The review team did not find adequate data in the application to make any statement on the relative efficacy of dofetilide and other antiarrhythmic agents (sotalol, quinidine or propafenone). Dosing information will be discussed below after safety considerations.

Despite a conclusion that overall the clinical trials did find a treatment effect for dofetilide in converting to and maintaining NSR, it is not as easy to translate these efficacy measures into real patient benefits with direct evidence in the NDA. In contrast to the rhythm control, **symptomatic benefits** of dofetilide have not been a primary objective in the development program and the data are much less persuasive. Although patients who were maintained in NSR fared better (vs those who relapsed) numerically in exercise test (Study 120X) and in symptomatology scores, the data were flawed with small sample size, high variability and problems of multiple comparison. If it is true that patients in NSR are less symptomatic (most likely, although no solid data) and since there were more dofetilide patients who remained in NSR, it will then be difficult to understand why there was no significant treatment effect across different groups. One possibility is that patients who received but did not respond to dofetilide felt much worse than the placebo group (mostly relapsed) to pull down the overall score for the dofetilide group. Thus, dofetilide should not be given an explicit claim for symptomatic benefit. But in view of all the serious complications of anticoagulant treatments and rate controls for AF/AFl, maintenance of NSR should not be considered as a non-approvable surrogate endpoint completely devoid of clinical meaning.

Paroxysmal SVT and SVA

Unlike that for chronic atrial arrhythmias, the efficacy of dofetilide for paroxysmal SVT and SVA has not been as well-established. As described above, only Study 372 showed a statistically significant effect of dofetilide in preventing further pSVT attacks. Another good size study in pSVT (Study 119) failed to distinguish dofetilide (at slightly lower doses of $\leq$375 mcg bid) from placebo in a mixed group with a small percentage of patients having pSVT (18%, the rest had pAF/pAFl). Thus the second study (Study 119) did not contradict nor confirm the former smaller, foreign trial (Study 372). It should be noted that, however impressive the p-values were (0.001) for results of Study 372, the reviewers are not comfortable assigning this isolated study the same weight as two trials with confirmatory positive outcomes. Worse than not having additional support, this doubt on efficacy in pSVT was instead heightened by the failure of all other studies on pAF/pAFl to show even a marginal effect favorable for dofetilide. The reviewers are therefore not convinced that the effectiveness of dofetilide in pSVT has been demonstrated conclusively.

ADVERSE EXPERIENCES AND RISK OF TREATMENT

The Safety Database

While the total number of patients in the entire clinical development program was large (9,110), not all are directly useful in the safety assessment of dofetilide as a treatment of chronic AF/AFl (Section 2.2 of Dr. Gordon's Review). Excluding those of non-targeted populations (healthy subjects), inadequate exposures (short-term, single dose, intravenous/oral clinical pharmacology studies), and Japanese trials (analyzed separately), the following datasets may be considered more relevant for safety analyses (all using oral dofetilide):

Phase II/III only	Dofetilide	placebo	active controls	Total
SVA controlled	1377	677	235	2289
VT/VF controlled	398	101	250	749
Open/Uncontrols#	210	0	0	210
subtotal	1985	778	485	3248
DIAMOND Studies	1511	1517	0	3028
Total	3496	2295	485	6276

VT/VF studies only, there were no open/uncontrolled Phase II/III studies in SVA.

For most of analyses of adverse effects, the sponsor combined the SVA and ventricular arrhythmia (VA) phase II/III studies and teased out truncated, smaller studies to form a "relevant studies" (mostly efficacy trials) subset:

SVA & VA Phase II/III	Dofetilide = placebo controlled+active/no control	placebo	active controls
total treated	1941=1479+462	778	496
relevant studies	1776=1418+358	759	476

A great majority of patients were randomized to 250 or 500 mcg bid, with a provision for downward titration in most studies (see below in dosing information), and treated for a mean duration of 5-6 months (mean 20-24 weeks for $\leq$ 500 mcg bid) (see Sections 2.2 & 2.5 of Dr. Gordon's review). About 15% of patients in SVA studies actually received 500 mcg bid for one year or longer.

As expected from its pharmacological activities (inhibition on the potassium channel and delay in cardiac repolarization), proarrhythmic effects are the most prominent safety concerns of dofetilide treatment. In addition to the analyses of all SVA studies, experiences from a large mortality trial (the DIAMOND Study) in patients with congestive heart failure (CHF) or recent myocardial infarction (MI) (but not necessarily with atrial arrhythmias) will be incorporated into the discussion below. For regulatory deliberations, published historical data of quinidine will also be considered to assess the relative safety of dofetilide.

The DIAMOND Studies

As described in details by Dr. Williams, the DIAMOND Studies are double blind, placebo-controlled trials to evaluate the effects of dofetilide on mortality and morbidity in patients with left ventricular dysfunction (DIAMOND-CHF) or recent MI (DIAMOND-MI). The highlights of the studies, as relevant to the safety analyses for the intended use in SVA, are summarized as follows:

i) Total of **3,028** patients were randomized:
1518 in CHF (762 dofetilide, 756 placebo)
1510 in MI (749 dofetilide, 761 placebo)

ii) A great majority of patients in both studies had clinical heart failure (85-90% in NYHA Classes II/III), which is slightly more severe (more in Class III) in the CHF substudy. Only **17%** of the patients had **AF/AFl** at baseline, thus dofetilide was not intended to treat SVA in this trial and the overall patient population are different from that of proposed indication. Further, there were substantially more patients with AF/AFl at baseline in DIAMOND-CHF (26%) than in DIAMOND-MI (8%).

iii) Dofetilide was started at **500 mcg bid**. Dosage was reduced for patients with AF/AFl at baseline (to 250 mcg bid), for creatinine clearance lower than 60 ml/min and for excessive QT prolongation (see Dr. Williams' review for details). Patients were supposed to be followed until at least one year after the last recruits were admitted, The studies were completed in about 3 years for CHF (median follow-up 12 months) and 3.5 years for MI (median follow-up 15 months).

iv) The primary hypothesis of the DIAMOND Studies was that dofetilide reduces mortality in patients with CHF or recent MI, with **all cause mortality** (time to death) as the primary efficacy endpoint (see Dr. Cui's review for statistical design issues). Other mortality/ morbidity measures were specified, which included hospitalization for CHF and analyses of the AF/AFl subset, but all secondary in statistical designation.

v) Total of **1417** patients completed the studies (about 40% of CHF and 50% of MI subjects) and **647** died by the last clinic visit date*. Of the remaining patients who were lost to follow-up or discontinued for various reasons, there were additional **454** deaths occurred prior to the end of study (Tables 15-18 of Dr. Williams' review). Thus the overall mortality in the DIAMOND Studies was about 36% (about 1/3 were arrhythmia related in all groups, Table 39, Dr. Williams' review).

vi) Either in the CHF or the MI substudy, the probability of **survival** was almost **identical** in dofetilide treated patients and in those who received placebo (for details, see below and Section 9 of Dr. Williams' review), with nearly superimposable Kaplan-Meier curves for different treatment groups (Figures 3 & 4, Dr. Williams' review). There were fewer events in the "On-treatment" (OT) analyses, but the treatment effect was essentially the same as in the intent-to-treat (ITT) analyses. Careful reviews and re-analyses by Drs Williams and Cui did not reveal any serious disagreement on the numbers to challenge this conclusion.

vii) Since the primary hypothesis was rejected by the efficacy results, all other statements derived from the DIAMOND trials are only descriptive and of no statistical significance.

Serious ECG Effects

There is little doubt that dofetilide causes **QT/QT$_c$ prolongation****, which is clearly dose and plasma concentration dependent (see Clinical Pharmacology above) and was the reason for withdrawal in 3.9% of dofetilide patients (vs 0.1% in placebo, SVA studies only). The changes in QT$_c$ intervals in the "relevant set" studies (see above) are summarized as follows:

QTc increase from baseline	dofetilide# N=1304	dofetilide## N=247	placebo N=661	active control N=390
by 15-25%	21.3%	23.5%	6.2%	17.7%
by >25%	7.6%	9.7%	2.6%	2.1%
mean change	32 ms	43 ms	-2 ms	19 ms

Placebo controlled trials. ## Active or non-controlled studies.

Similar degrees of QT/QT$_c$ prolongation were also observed in patients with significant cardiovascular morbidity as in the DIAMOND studies (see Figures 30-36, Dr. Williams' review).

* The last clinic visit dates were variable for each patient and different from the fixed "end of study" date (EOS date, Dec 10, 1996).

** Correction for heart rate may be difficult in patients with AF/AFl, thus QTc analyses may have smaller denominators (see Dr. Gordon's review and Sponsor's fax on 12/4/98).

Heart rate was decreased modestly (-6 bpm) by dofetilide, possibly due to normalization of rhythm after AF/AFl. However, bradycardia may increase risk of QT related proarrhythmia (Roden, DM, PACE 1988, 21:1029)

Proarrhythmic Events

Not surprisingly, because of its effects on repolarization and QT intervals, various proarrhythmic events (see definitions in Dr. Gordon's review, Section 3.2) have been reported in patients treated with dofetilide. And the incidence* appears to be higher than that in the placebo controls, mostly due to the increase in torsades de Pointes (TdP).

Proarrhythmias	dofetilide N=1776	placebo N=759	active control N=476
TdP	**1.4%**	**0.0%**	**0.0%**
new sustained VT	0.3%	0.1%	0.8%
new VF	0.2%	0.1%	0.2%
any of above	**1.9%**	**0.3%**	**1.1%**

(relevant Phase II/III SVA & VA studies, see above)

The incidences of these proarrhythmias increase with dose, either randomized or actual, in the SVA studies (data shown in the Table below are by actual dose):

Proarrhythmias in SVA studies	dofetilide <250 mcg bid N=357	dofetilide 250 mcg bid N=497	dofetilide 500 mcg bid N=426	dofetilide >500 mcg bid N=33	dofetilide all dose N=1331	placebo N=672
TdP	**0.0%**	**0.6%**	**1.2%**	**6.1%**	**0.8%**	**0.0%**
VF	0.0%	0.2%	0.7%	3.0%	0.4%	0.1%
VT	3.5%	3.2%	2.8%	9.1%	3.3%	2.4%

In such studies, there appears to be a steep increase in overall incidence from approximately 5% at 500 mcg bid (426 actually received it) to around 18% at doses above 500 mcg bid (with only 33 subjects in the latter, from Tables in Section 3.2, Dr. Gordon's review). The frequency of TdP also increases with bioavailability of dofetilide (AUC and C_{max}) in the population kinetics studies.

Proarrhythmias seemed to occur at a higher rate in patients with ventricular arrhythmias (2.5% of 443 reported TdP, Dr. Gordon's review). In patients with cardiac dysfunction as in the DIAMOND studies, TdP was also more frequent in the dofetilide treated groups:

DIAMOND Studies	CHF		MI		Overall	
	Dofetilide N=762	placebo N=756	Dofetilide N=749	placebo N=761	Dofetilide N=1511	placebo N=1517
TdP	**25 (3.3%)**	**0**	**7 (0.9%)**	**0**	**32 (2.1%)**	**0**
VT/VF#	132 (17.3%)	114 (15.1%)	100 (13.4%)	103 (13.5%)	232 (15.4%)	217 (14.3%)

\# events, not patients; including those reported only by the investigators (not qualified by committee).

* As noted by Dr. Gordon, there are additional cases (5 dofetilide, 1 placebo) which were considered proarrhythmia by the investigators but did not meet the protocol specified definition. The incidence may also be underestimated because more dofetilide patients discontinued for QT prolongation (see above).

Thus, serious drug-induced proarrhythmias (TdP) appeared to be more common in sicker patients ($\geq$ 2.5%), such as those in the ventricular arrhythmia studies and in the DIAMOND-CHF trial. It occurs less frequently (approx. 1%) in relatively healthier subjects in AF/AFl and DIAMOND-MI. These are compared to zero case reported in the placebo and active control groups.

As Dr. Gordon pointed out in her review, not all proarrhythmias developed within the first 3 days of dosing with dofetilide. There were cases of TdP reported after 7 days and the risk remained throughout the studies despite dosage adjustment for various risk factors (renal functions and QT intervals).

Not surprisingly, the risk of TdP increases with the degree of QT/QT_c changes from baseline, in either AF/AFl or DIAMOND studies (Section 3.2.2, Dr. Gordon's review). Cases of TdP were reported for AF/AFl patients who had >20% increase from baseline in QT_c and for DIAMOND patients, even with smaller increases (10-20%) in QT_c. Long absolute QT interval at baseline is also predictive of pro-arrhythmic events, with an 8-fold increase in TdP for QT > 450 ms. Despite careful screening in most dofetilide studies to exclude patients with QT >440 ms, TdP still occurred. Thus it may not be realistic to expect that requiring prescreening for long QT in the labeling will eliminate the problem in the practical setting. Other univariate analyses suggested that TdP was more frequent in females (risk ratio to male: 3.77 [95% confidence interval 1.74-8.17]), patients with structural heart diseases (risk ratio to those without: 2.32 [0.96-5.63]) and primary diagnosis of VT (risk ratio to those with SVA: 2.9 [1.27-6.61]). Of these, gender and baseline QT were confirmed by multiple logistic regression analyses.

Mortality

While it is clear that dofetilide treated patients have increased risk of serious proarrhythmias such as TdP, it is less evident whether this adverse effect would lead to higher mortality. In 2,748 subjects who received dofetilide in clinical studies (excluding DIAMOND), total of 94 (3.4%) died within or beyond 7 days of stopping treatment. Of these, 37 deaths occurred in uncontrolled VT/VF studies. In the remaining, the numbers of patients who died within 7 days of stopping the study drugs are summarized as follows :

Deaths (Excluding DIAMOND Studies)

Deaths ≤7days	Dofetilide vs placebo		Dofetilide vs active controls	
SVA controlled	**11 (0.8%)**	**2 (0.3%)**	**1 (0.2%)#**	**0**
VT/VF studies	2 (2.0%)	2 (2.0%)	8 (2.7%)	4 (1.6%)
iv studies	1 (0.1%)	1 (0.2%)	1 (0.2%)	0
clin pharm	1 (0.3%)	0	0	0
Total	15 (0.6%)	5 (0.3%)	10 (0.6%)	4 (0.5%)

including dofetilide groups from studies with placebo arms, thus partially redundant with the dofetilide number in placebo controlled trials.

In the above table, only the deaths in SVA studies are informative and relevant to the proposed indication to treat AF/AFl. For the later deaths (after 7 days of stopping medication), all but one (26 days) were beyond one month and 3 were after 1 year. They are therefore deemed irrelevant and not included in the survival analyses below. Most of the deaths (>60%) were classified by the sponsor's consultant as sudden cardiac, arrhythmic or presumed arrhythmic, deaths (SUCD).

Survival analysis performed by Drs Edward Pritchett and William Wilkinson (commissioned by the sponsor) provides some estimates of the relative mortality risk for patients receiving dofetilide in placebo controlled studies in chronic or paroxysmal SVA:

Survival Analysis	mortality rate		dofetilide vs placebo	
	Dofetilide	placebo	hazard ratio	95% CI
AF/AFl + pSVT	0.9%	0.4%	1.4	0.4, 5.1
adjusted#			1.1	0.3, 4.3
excluding pSVT	0.9%	0.3%	1.9	0.4, 8.6
adjusted#			1.4	0.3, 6.9

adjusted for potentially confounding factors of age, gender, primary diagnosis and presence of structural heart diseases.

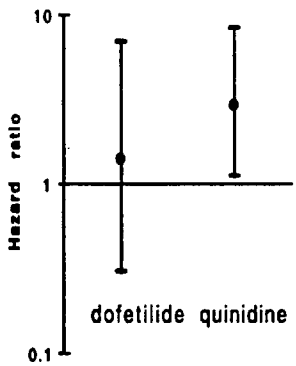
While the difference is by no mean near statistical significance ($p>0.4$), the trend did favor placebo and one cannot rule out confidently a 4-8 times higher mortality for patients who are treated with dofetilide (vs placebo) for SVA's. For Kaplan-Meier survival curves, see Section 4.1.1 of Dr. Gordon's review.

This estimated mortality risk of dofetilide has been compared with that of quinidine, the only antiarrhythmic agent currently approved for treating chronic AF/AFl, including patients with structural heart disease. Of note, the quinidine meta-analysis was based on slightly smaller size of sample (about 800 patients, Coplen, et al., Circulation 82:1106, 1990).

Risk vs placebo	hazard ratio	95% CI
dofetilide#	1.4	0.3-6.9
quinidine	2.98	1.1-8.3

excluding pSVT, adjusted (from table above)

As also shown in the diagram on the right, although dofetilide has a lower boundary across ratio of one, there is still a large uncertainty about excessive risk and the upper limits of confidence interval were similar for the two drugs. Thus the comparison does not lead to a conclusion that dofetilide may not be as dangerous as quinidine. Besides, the reviewers are also concerned about the comparability of the two sets of studies in the meta-analyses (e.g., quinidine studies were conducted prior to 1985).



Despite that the study population are not the same as in the trials of uncomplicated AF/AFl, experiences from the **DIAMOND studies** may be useful for further mortality assessment. The sponsor considered it reassuring that mortality rates in dofetilide treated patients with more severe cardiac morbidity were not higher than that in the placebo groups in DIAMOND. As summarized in the following table, the probabilities of survival were nearly identical in both treatment groups in DIAMOND, with remarkably narrow confidence intervals around risk ratio of one (dofetilide:placebo) (Table 20 of Dr. Williams' review and Tables 4.1, 4.2 of Dr. Cui's statistical review):

DIAMOND Studies	CHF			MI		
ITT	Dofetilide N=762	placebo N=756	p	Dofetilide N=749	placebo N=761	p
death (%)	311 (41%)	317 (42%)	0.557	230 (31%)	243 (32%)	0.226
prob. survival	0.73	0.72		0.79	0.77	
risk ratio (95% CI)	0.95 (0.82, 1.12)			0.92 (0.77, 1.11)		

For those patients with AF/AFl at baseline in DIAMOND, there was no treatment difference in mortality either (Table 4.4, Dr. Cui's review):

DIAMOND AF	CHF/MI		
ITT	Dofetilide N=249	placebo N=257	p
death (%)	111 (45%)	116 (45%)	0.98
risk ratio (95% CI)	1.00 (0.77, 1.29)		

However, the reviewers are not so convinced that the DIAMOND study findings are supportive of dofetilide safety in chronic AF/AFl. Instead, there is evidence from DIAMOND suggesting the contrary and the results deserve further dissection.

First, it should be noted again that the only valid statistical conclusion from DIAMOND is that the study *failed to distinguish dofetilide from placebo* in mortality. This is not the same as proving "dofetilide is *equivalent* to placebo". Thus, as the 95% CIs of risk ratio indicate, one cannot rule out a 11-12% (and 29% for those with AF/AFl) increase in mortality risk for dofetilide.

Secondly, the risk of proarrhythmic deaths in dofetilide treated patients may be masked by an improvement in heart failure in the DIAMOND studies. The data from the CHF (but not MI)* substudy suggest that while its mortality effect is neutral, dofetilide may reduce hospitalization for worsening heart failure** (Tables 4.1 and 4.4 of Dr. Cui's review):

	DIAMOND CHF			DIAMOND AF (MI+CHF)		
Hospitalization for CHF	Dofetilide N=762	placebo N=756	p	Dofetilide N=249	placebo N=257	p
≥ 1 episode	229 (30%)	290 (38%)	0.002	73 (29%)	102 (40%)	0.009
risk ratio (95% CI)	0.76 (0.64, 0.90)			0.67 (0.50, 0.90)		

In the overall population (CHF+MI)*, the benefit seemed to be concentrated in those patients who had AF/AFl at baseline (see Table above). When patients without such SVAs were excluded, the treatment difference on worsening of heart failure disappeared (see Dr. Cui's review).

* As noted above in the summary, the MI substudy was less populated (8%) with AF/AFl, contributed less than one quarter of AF/AFl subset.

** Again, reduction in CHF hospitalization is a secondary finding, its significance must be viewed in the context of a failed primary objective (mortality).

Since in most recent large trials of heart failure, decreases in hospitalization were usually associated with reduced mortality, it is thus puzzling that the latter was missing in the DIAMOND (esp. CHF) studies. One possibility is that there may indeed be a survival benefit in maintaining NSR for CHF, but there was also an increase in deaths due to the proarrhythmia of dofetilide treatment. And the net result from the two opposite effects was a neutral finding in mortality as seen in DIAMOND. On the other hand, in patients with uncomplicated AF/AFl, i.e., those without heart failure, the presumed survival benefit from reduced CHF-related morbidity will be absent but the risk of proarrhythmic death remains.

Another equally or more plausible explanation is that the high overall mortality in the DIAMOND studies (36%) totally obscured a small risk of excessive proarrhythmic deaths (e.g., 1%) in the dofetilide groups. In a large population with uncomplicated AF/AFl and a low background death rate, such a small adverse effect on mortality will appear prominent and intolerable.

Thus, in either case, the DIAMOND experiences do not alleviate the concern that dofetilide may have a 4-8 times of excessive mortality in patients treated for chronic AF/AFl (see above survival analyses above for non-DIAMOND studies in SVA).

The DIAMOND data also suggested that the conflicting benefit and risk of dofetilide were only observed in patients with AF/AFl. In patients without SVA as in DIAMOND-MI (only 8% had AF/AFl at baseline) or DIAMOND-non AF (CHF+MI but excluding AF), dofetilide did not have an arrhythmia (AF/AFl) to treat, did not reduce hospitalization for heart failure, and had no apparent excessive mortality (see also above for other explanation). The paucity of AF/AFl patients in DIAMOND-MI helps explain why patients in the MI substudy had responded to dofetilide differently than those in DIAMOND-CHF or DIAMOND-AF, and why the DIAMOND-MI results cannot be applied to patients with uncomplicated chronic AF/AFl*.

Other Serious Events & Withdrawals

In the placebo-controlled SVA studies, about 27% of dofetilide patients reported a **serious adverse event**, which is compared with 29% in the placebo groups. Other than those related to proarrhythmia described above, few serious events, clinical or laboratory, occurred at ≥1% and were more frequent in dofetilide than in placebo (sponsor's amendment of 12/24/98). A nominal difference in total neoplasm (2.1% dofetilide vs 0.9% placebo) was seen in pooled SVA trials (but not in DIAMOND studies). Specific tumors were rare and the observation is most likely due to longer duration of follow-up for the dofetilide group.

More than 40% of dofetilide-treated patients were **withdrawn** for various reasons in Phase II/III studies, which was not significantly different from that of comparative groups. For specific reasons of withdrawals not related to proarrhythmias, there was no alarming dose-related trend** or imbalance between treatment groups. Detailed analyses of serious events and withdrawals are referred to Dr. Gordon's safety review (Pages 63-68). There were isolated cases of withdrawals for laboratory abnormalities, but there was no evidence in number of cases or case descriptions suggesting a pattern or clear causal relationships (Section 6.1, Dr. Gordon's review).

* Although the rates of TdP were similar in SVA studies and in DIAMOND-MI (see Proarrhythmic Events above), relative mortalities (vs controls) may still be quite different (see 95% CIs of risk ratios).

** As noted by Dr. Gordon, discontinuations because of QT prolongation appeared to decrease with dose. This may be due to dose reduction in the high dose group for QT interval instead of immediate withdrawal.

Non-serious Effects and Tolerability

Other than the adverse experiences related to proarrhythmia, dofetilide appeared to be as tolerable as controls in patients treated for SVA. Complaints which were more frequent in dofetilide than in placebo were mostly non-specific with a small treatment difference, as summarized in the table below for those events with (dofetilide-placebo) differences of $\geq$1%*. Similar profiles of non-serious adverse experiences were observed for the subgroup randomized to 500 mcg bid in SVA studies, in the population pooling SVA and VA studies, and in DIAMOND trials**. Direct comparative data were limited and there was no serious attempt to claim superior tolerability of dofetilide over that of quinidine (see also below on relative safety).

	SVA Studies (%)	
ADE	dofetilide N=1331	placebo N=672
Any subjective	59.9	54.0
Any objective	28.6	32.1
chest pain	9.6	6.7
flu syndrome	3.5	1.6
resp track inf	6.5	4.8
accident injury	2.9	1.2
headache	10.7	9.1
dizziness	7.7	6.3
dyspnea	6.2	4.8
back pain	3.1	2.1

(ranked by difference between dofetilide and placebo)

Except for proarrhythmia related abnormalities, dofetilide treatment did not in general have any significant effect on the group averages of other **objective** or **laboratory** parameters.

Mild-to-moderate decreases (defined as $\leq$60% by the sponsor) in **hemoglobin/ hematocrit** were reported in more male dofetilide-treated patients than in the male placebo group (2.5-2.7 % vs 0.6-0.9%, Page 84, Dr. Gordon's review), but none were discontinued from the study and the difference was not seen in female subjects nor in the DIAMOND studies. Most of the decreases were not severe (20-30%, one patient had a 50% drop due to warfarin-related retroperitoneal bleed), and reviews of case reports did not suggest any causal relationship with dofetilide. Five patients treated with dofetilide had platelet counts <50,000 (vs 1 in placebo), but the abnormal values appeared to be either pre-existing or spurious in nature. Other hematological parameters were not affected.

While the mean values of **liver function** tests were not affected by dofetilide and the number of subjects with marked elevation was no different between groups, changes from baseline in liver enzymes increased modestly with dosage of dofetilide (see Table on Page 87, Dr. Gordon's review). Since the changes were small at 500 mcg and below (<5$\pm$1.3)

* excluding "application site complications" and "procedures"

** In DIAMOND-CHF (26% with AF/AFl), peripheral vascular disorders, constipation, dizziness and hematuria were more common in dofetilide groups.

and few were considered serious, strong warning in the labeling is probably not required. Electrolyte, renal function and lipid/glucose related **blood chemistry** tests were not affected by dofetilide, but data and analyses for bicarbonate or urinalyses were inadequate.

As noted above (in ECG effects), dofetilide may decrease heart rates mildly. It does not have appreciable effects on blood pressure.

Safety in Patients Subgroups

The **age** effect on safety of dofetilide is somewhat sketchy in the NDA database and some of the phenomena may be partly due to lower renal clearance in the elderly. In the "relevant studies" set (Page 94, Dr. Gordon's review), degrees of QT_c prolongation were higher in the elderly. But such age dependence for QT_c changes was not observed in the clinical pharmacology studies and rates of proarrhythmic events were not apparently age related (Tables on Page 93, ibid). On the other hand, in the sponsor's analyses for both Phase II/III and DIAMOND studies, TdP increases numerically with age, although such relationship was not statistically significant. Age is not an independent risk factor for other adverse experiences.

It is well known that female patients are in general more susceptible to drug-induced proarrhythmic effects (Makkar, R., et al. *JAMA*, 1993, 270:2590). Data in this NDA suggested that dofetilide is of no exception with respect to this **gender** difference and risk/benefit in female may be less favorable than that in male subjects. While the bioavailability were only modestly higher in female (10-15% in AUC and 20% in C_{max}, see Clinical Pharmacology) and there was no appreciable difference in mean QT_c changes, proarrhythmic events were clearly more frequent in the female patients (note that in the following safety datasets,*there were no reports of TdP in any of the placebo groups, male or female*, see Pages 98-102, Dr. Gordon's review):

TdP in	male	female
SVA studies	0.3% (3/889)	1.8% (8/457)
Phase II/III	0.8% (11/1392)	2.9% (16/549)
DIAMOND# (CHF+MI)	1.6% (17/1088)	3.5% (15/423)

both pre- and post-implementation of dose adjustment for creatinine clearance.

In the DIAMOND studies, dose adjustment for creatinine clearance appeared to reduce the incidence of TdP in female patients (from 9.6% to 2.3%, see Table 42 of Dr. Williams' review). This propensity did not lead to a higher overall drop out rate in the female subjects, and there is no strong evidence suggesting that women treated with dofetilide for SVA may have higher rate of sudden and unexpected cardiac deaths (SUCD). There is no other gender related safety issue except that oral contraceptives (OC) and possibly, hormone replacement therapy (HRT), may have clinically important interactions with dofetilide (see Clinical Pharmacology).

There were too few minority patients (38 blacks) in the safety database to allow any meaningful assessment of safety in different **racial** groups.

Without direct analyses of adverse experiences in patients with different **underlying diseases**, there are some legitimate concern that QT_c prolongation (and hence proarrhythmia) will be more of a risk in patients with **renal** impairment, possibly through lower dofetilide clearance and higher blood concentrations (see Clinical Pharmacology). QT_c prolongation was slightly greater in the patients with moderate **hepatic** dysfunction (mean changes of 26.3±7.5 ms vs 12.3±6.4 ms in healthy subjects, Section 8.5, Dr. Gordon's review). Since clearance of dofetilide was not affected, the reviewers were not very anxious to recommend dose adjustment for such patients. However, it is not clear whether patients with more severe impairment would have more exaggerated QT prolongation and proarrhythmic effect. Although there is no clear evidence that dofetilide treatment causes further hemodynamic deterioration in patients with **left ventricular dysfunction** (it may actually reduce hospitalization for CHF, as shown in DIAMOND), structural heart disease is a risk factor for proarrhythmias (see above). Whether safety issues related to these confounding disease states and potential drug-drug interactions through common metabolic pathway can be adequately and practically addressed in the labeling should be considered before approval of the NDA is granted (see below on "Dosing Information and Instructions for Use").

There is no evidence that dofetilide treatment causes any problem in tolerance or rebound after withdrawal. The 3 cases of overdose (to 500 mcg x2 within 1 hour) in clinical trials have provided limited advice for management (see Section H.6.G of NDA). Activated charcoal may be used to reduce absorption in overdose (Study 246). The drug has not been used in pregnancy.

Safety relative to other Antiarrhythmics

Neither the sponsor nor the reviewers think that the clinical data support any specific claims of relative safety/tolerability compared to that of other antiarrhythmic agents. Aside from the usual problems of isolated, small size studies not comparing full dose range in active controlled trials, such studies in the dofetilide program were conducted in populations with different types of SVA/VA which may not be relevant to the proposed indication (e.g., vs quinidine in pAF/pAFl) and many active comparators have not been approved by FDA for the same indication (e.g. vs sotalol for chronic AF, despite common off-label use). The comparative studies are thus of limited use in regulatory deliberation of the application and there are no analyses of relative risk/benefit among the different agents to provide guidance in the practical settings.

There were no prominent, favorable or unfavorable, differences in adverse experiences between dofetilide and sotalol (Study 345) or propafenone (Study 372, pSVT). Compared with those received quinidine 300 mg bid in a small pAF/pAFl study (about 50 patients per group, treated for 6 months), patients on dofetilide 250 mcg bid reported less of the following adverse events (ranked by the difference between groups):

	Study 363 (%)	
ADE	dofetilide N=48	quinidine N=57
Digestive total	8.3	33.3
diarrhea	2.1	19.3
abdominal pain	0.0	12.3
palpitation	16.7	28.1
headache	4.2	14.0
asthenia	22.9	31.6
dyspnea	14.6	21.1

Although this study was in paroxysmal SVA, there is no reason to believe that this contrast between the two drugs (in gastrointestinal symptoms) will be different in chronic AF/AFl patients. Dofetilide may also cause less palpitation, headache and asthenia. However, there were more discontinuation due to "objective test findings" (possibly ECG results) in the dofetilide group (23% vs 12% for quinidine) and there were no differences in percentages of patients who had reported adverse events, serious or severe events, or discontinued due to adverse events (Table 7.1 of Study 363 Report). Thus, based on this small sample, overall tolerability of dofetilide appeared to be similar to that of quinidine.

Safety during Acute Conversion

When used as a treatment to convert AF/AFl to NSR, there were no alarming safety issues during the 3 day, closely watched in-patient period (see Section 12.0 of Dr. Gordon's review). Other than non-specific complaints (headache, dizziness, nausea and bronchitis), VT, AV block and bradycardia were prominent adverse experiences, which were reported and led to withdrawal at approximately the same rates in almost all treatment groups (2-5%, slightly higher in the 500 mcg bid group, and lower in the placebo group in Study 345).

Japanese Studies and Safety Update

For the 610 patients from 18 Japanese studies not included above and 243 patients from 9 protocols in the Safety Update (to 01/05/98), the profiles of adverse experiences were similar to that of the rest of clinical studies (see Sections 11 and 14, Dr. Gordon's review).

Dosing Information and Instructions for Use

Dosage Recommendations

Because of the narrow window between effective doses (250-500 mcg bid) and doses with excessive risk of TdP (>500 mcg bid), clinical trial protocols have been designed or revised to start at 500 mcg bid and allow downward dose adjustment for QT_c prolongation and low creatinine clearance. The reviewers were concerned initially that the randomized and actual doses may be different and efficacy/safety analyses based on randomized dosage may be misleading. Nevertheless, if the patient demographics in clinical trials are representative of the general population and the drug can be prescribed in the same manner as that used in the clinical studies, i.e., adjusting dose with ECG and creatinine measurements for all patients, then the clinical trial experiences (based on randomized dose) should reflect that of general use. Accordingly in the package insert, the sponsor recommends a usual initial dose of 500 mcg bid for patients with chronic AF/AFl, which may be reduced as follows:

Cr Clearance#	w/o QTc prolongation	w/ QTc prolongation##
>60 ml/min	0.5 mg bid	0.25 mg bid
40-60 ml/min	0.25 mg bid	0.125 mg bid
20-40 ml/min	0.125 mg bid	0.125 mg qd
<20 ml/min	individualized	(discontinued)

\# calculated using Cockcroft's formula

\## QTc >500 ms or >15% increase from baseline, use QT if heart rate < 60 bpm (see labeling)

The sponsor suggests that dofetilide be given in a hospital setting and under monitoring for at least 5 doses of dofetilide or 12 hours after conversion to NSR, whichever is longer.

For patients with AF/AFl and left ventricular dysfunction, dofetilide was started at a lower dose of 250 mcg bid in the DIAMOND trials. However, dofetilide has no inotropic effect on myocardium and there is no biological/demographical reason nor evidence from actual clinical experiences suggesting that DIAMOND AF patients could not tolerate the starting dose of 0.5 mg bid as in the rest of DIAMOND studies. Thus the above dosage adjustment scheme should apply if dofetilide is approved only for treating AF/AFl in patients with left ventricular dysfunction, as recommended in this memo (see Recommendation below).

Even if the above scheme is not too complicated to follow for the initial treatment in the hospital, a practical question is how frequently the creatinine clearance and QT_c intervals should be monitored in subsequent course of chronic oral therapy. It should be noted that creatinine clearance/ECG parameters may change during long-term follow up and not all proarrhythmias occurred within the first few days of dosing. Whenever it is medically indicated to measure these parameters, it will require the attending physicians, while managing complex clinical problems, to remember adjusting dofetilide dosage accordingly.

Dosage recommendation and adjustment to minimize proarrhythmic risk are therefore no trivial matters for dofetilide, although one may argue that the proposed scheme is justified by the complexity of the disease to be treated and the scarcity of alternative effective and safe therapies. Whether such elaborated prescription instruction can be followed effectively in the practical settings, however, is a safety concern.

Special Populations

While the higher risk of proarrhythmia for **female** patients is not specific to dofetilide, it may be difficult to use the drug in women. In addition to adjustment for renal clearance, baseline QT intervals and body weight, further dosage reduction should be considered for female patients, especially those who may be taking oral contraceptives or hormone replacement therapy, as well as other medications which may interact with dofetilide (such as ketoconazole, see Clinical Pharmacology above and Drug Interactions below).

There are no clinical trials assessing the efficacy or safety of dofetilide in **pediatric** patients, either completed or in progress. The sponsor claimed that the drug has little potential for use in children and thus did not commit to any study in children. Dofetilide appeared to be effective in patients age 65 years or older, there are no apparent age-related safety issues in the **elderly**.

There are not enough data to differentiate use of dofetilide among different **racial** groups.

In addition to the dose adjustment described above for patients with **renal** impairment, dofetilide should be used with caution in patients with severe **hepatic** dysfunction. Although clearance of dofetilide was not affected in the moderately impaired and the reviewers do not feel dose adjustment for such patients based on a modest increase in QT_c intervals is necessary (see above in Safety), it is not sure whether patients with *severe* impairment would have more exaggerated ECG response and increase in proarrhythmic events.

Drug & Food Interactions

Since dofetilide is a substrate of cytochrome P450 3A4 system, potential kinetic interaction with other metabolic substrate is a notable safety concern. **Drug-drug interactions** were assessed in several studies, describing both the kinetic effects of other agents on dofetilide blood concentrations and the effect of dofetilide on other agents (see Dr. Fadiran's biopharmaceutical and Dr. Gordon's safety reviews). While the drug interaction studies were not as thorough as one preferred (except for the study on oral contraceptives and ketoconazole, all other drug interactions were studied only in male subjects), there are enough data to justified a strong warning in the labeling. Whether the prescribing physicians will heed this advice in the practical setting, however, is another issue which may require intensive educational effort.

A slight delay in absorption was observed when dofetilide was administered with **food**, which is not likely to be clinically important.

CONCLUSIONS/RECOMMENDATIONS

Dofetilide has been shown to be an effective antiarrhythmic agent for acute conversion and maintenance therapy in chronic AF/AFl. Evidence of efficacy based on rhythm control is convincing and the implied clinical benefit of NSR is a reasonable conjecture, although one would wish for more concrete data on symptomatic relief in the application (thus no specific symptomatic claims). While the benefit and risk of using dofetilide for acute conversion is not difficult to determine (and therefore approvable as proposed), the reviewers are not comfortable to recommend approval of chronic oral therapy for patients with non-complicated AF/AFl (i.e. without left ventricular dysfunction). On the other hand, the risk/benefit ratio is more acceptable, and thus the indication more approvable, for patients with chronic AF/AFl *and* heart failure (the DIAMOND-AF patients). The concerns are basically about safety and the reasonings are summarized as follows:

1. It is not clear the benefit of maintaining NSR, thus avoiding the complication of other management options (anti-coagulation, etc) for chronic but uncomplicated AF/AFl, justifies the concern of QT/QT_c prolongation and a small but definite risk of life-threatening proarrhythmia (TdP).
2. Whether the risk of proarrhythmia is associated with an excessive mortality is difficult to determine precisely from the available data. Nevertheless, the uncertainty does not preclude a possibility that dofetilide may cause more deaths than placebo in chronic AF/AFl.
3. From the pooled survival analyses of AF/AFl studies (excluding DIAMOND), the 95% confidence intervals indicate that dofetilide may have an excessive mortality as high as 4-8 times of placebo.
4. The results of DIAMOND studies suggest that dofetilide may reduce CHF-related morbidity (hospitalization), such benefit was seen only in patients with AF/AFl (due to maintaining NSR?).
5. But a possible mortality benefit usually associated with decreased CHF hospitalization was not observed in DIAMOND, possibly masked by excessive deaths due to proarrhythmic effects of dofetilide.
6. Without a potential CHF-related morbidity/mortality benefit in patients with only uncomplicated AF/AFl, the risk of proarrhythmic death will be un-opposed.

7. Another explanation of the DIAMOND findings is that a low but excessive risk of proarrhythmic death (e.g. 1%) was totally obscured by the high absolute mortality in DIAMOND (36%). Without the noisy background rate in a large population with simple SVA, the excessive mortality risk may become apparent and intolerable.
8. Thus, in either case, the neutral finding in mortality in DIAMOND does not provide assurance about the safety of dofetilide and the uncertainty about excessive mortality from the survival analyses (in non-DIAMOND studies) remains. The uncertainty and fear cannot be dismissed lightly because of the real effect of serious proarrhythmias.
9. In addition, the instructions for use are complicated and may not be easy to follow in the practical settings. It requires monitoring of renal function and ECG changes for initial dosing and appropriate follow up for possible subsequent dose adjustment is yet to be defined. Special care is also needed in dosing for female patients, who appear to be much more vulnerable to developing TdP from dofetilide treatment (especially with potential drug interactions). This demand of precision in prescription to ensure appropriate use of the drug adds up to the burden on the attending physicians and raises the risk of medication errors. The consequence must be considered in overall risk/benefit assessment.
10. Because of the tight relationship between blood concentration and QT prolongation, as well as the narrow safety margin for proarrhythmia, potential interactions with other concomitant medications which share the common metabolic pathways may increase the blood concentration of dofetilide to a dangerous level (again, women may be at higher risk). The review team is not sure whether it is possible to provide adequate warning in the labeling to minimize this safety problem, based on recent experiences with other drugs such as mibefradil.
11. On the other hand, for patients with heart failure, one is better assured that there is less likely an excessive mortality from the experiences in DIAMOND (narrower confidence intervals). For efficacy and other non-lethal safety issues, there are no surprising findings in this patient subgroup which may contradict that of non-DIAMOND studies and there is no reason that experiences in the latter cannot be applied to the AF/AFl-CHF subpopulation. These patients in general will be monitored much more closely because of their underlying cardiovascular morbidity. It is thus likely (and reasonably hopeful) that the set of elaborate instructions for prescription will be followed more diligently and the drug will be used more appropriately by the specialists.

To deny the use of dofetilide for uncomplicated AF/AFl patients (if there are such), the recommended regulatory action will have to be reconciled with the fact that quinidine is approved for the same indication and is widely used in current practice. Without a head-to-head direct comparison in the indicated population (chronic AF/AFl), it is difficult to assess the relative efficacy and safety of the two drugs. One may speculate from the available survival analyses that the mortality risk of dofetilide is probably no worse than that of quinidine (again, not a legitimate statistical exercise), and dofetilide may indeed be more tolerable than quinidine in gastrointestinal adverse effects. If this is true (and provided that dofetilide is not substantially less effective than quinidine), then there is no reason not to approve dofetilide for general use in chronic AF/AFl (i.e. not just for CHF patients with the arrhythmia).

However, if dofetilide is to be approved for this reason of equity, that is, if approval has to be based in part on the benefit/risk relative to those currently available, then instead of relying on an indirect and post hoc comparison with historical data, a prospective, full dose range comparative trial to evaluate efficacy and safety of the new and old drugs is preferred. While carrying out such active controlled trial may be a dauntingly difficult task, there is a public health need to re-evaluate

some of the existing treatments which were approved with ancient data from a less sophisticated era and have had a questionable risk/benefit ratio noted in later experiences. The suggested study will help resolve the issue and can be considered as a post-marketing requirement (after approval for a more restricted use).

Whether dofetilide is more effective and/or safer than other antiarrhythmic agents is not a regulatory issue at the present time, as most have not been approved for the same indication as the one being sought in this NDA (e.g. sotalol and propafenone).

It is therefore recommended that dofetilide be approved as a treatment of chronic AF/AFl , for acute conversion in general and for maintenance therapy in patients with left ventricular dysfunctions. It should not be used as a[illegible]

To be considered for less restrictive use, a direct comparison with currently approved drugs as suggested above is strongly recommended. Dofetilide should not be approved for

The draft labeling will be edited after the Advisory Committee meeting.

/S/

Shaw T. Chen, M.D.,Ph.D.

cc:
ORIG: NDA 20-931
HFD-110
HFD-110/Project Manager
HFD-110/Fenichel
HFD-110/Ganley, Gordon, Williams, Knudsen, Gill-Kumar, Resnick
HFD-710/Hung, Cui, Mahjoob
HFD-860/Fadiran, Marroum
HFD-110/SChen/01/19/99

revised 99/01/19, 10:40

Roeder

RHPM Review of Labeling

Application:	NDA 20-931 Tikosyn (dofetilide) Capsules, 125, 250 and 500 mcg
Applicant:	Pfizer Pharmacetuical Production Corporation Limited
U.S. Agent:	Pfizer Inc.

An approvable letter was issued for NDA 20-931 on March 5, 1999, in which the applicant was asked to submit final printed labeling. We met with the firm on numerous occasions to discuss the professional package insert and the patient package insert. We came to agreement with Pfizer regarding the text of the professional package insert in a telecon on July 19, 1999. Pfizer submitted the final printed professional package insert and carton and container labels in a submission dated September 8, 1999. They submitted a draft patient package insert in a submission dated September 15, 1999.

Review

The final printed profession package insert is identical to the draft that we had agreed to in the July 19, 1999 telecon with the following exceptions:

- Under **ADVERSE REACTIONS: Other Adverse Reactions**, the listing of adverse reactions that occurred >2% but no more frequently on Tikosyn than on placebo and ≤2% and numerically more frequent with Tikosyn than placebo were both presented alphabetically.
- Under **CLINICAL STUDIES**, all-cause hospitalization and hospitalization for worsening of heart failure data in the DIAMOND MI study have been incorporated into the package insert as agreed to with the Division.

The applicant was also given the choice of using mcg or mg as the primary unit of measure for dose. They chose to use mcg, and have incorporated it appropriately throughout the labeling. The firmed had formatted the **HOW SUPPLIED** section as a table, but the wording is somewhat awkward. Each sentence describing the capsules ends with "and are available in:" but should be changed to "and are available as described in the table below." The firm has agreed to make this change at the time of their next printing.

The patient package insert was submitted in draft. Any comments from the Office will be incorporated into the draft and included in the approval letter.

The approval letter will be drafted for approval on final printed professional package insert, final printed carton and container labels, and draft patient package insert.

/S/
David Roeder
Regulatory Health Project Manager

cc: NDA 20-931
HFD-110
HFD-110/Project Manager

ROEDER

RHPM Approval Overview

Application: NDA 20-931
Tikosyn (dofetilide) Capsules, 125, 250 and 500 mcg

Applicant: Pfizer Pharmaceutical Production Corporation Limited

U.S. Agent: Pfizer Inc.

An approvable letter was issued for NDA 20-931 on March 5, 1999. At that time, the following issues still had to be resolved:

1) Final printed labeling (including a patient package insert) should be submitted.

Resolution: We had numerous discussions with the applicant regarding the professional package insert and the patient package insert. The applicant has submitted a final printed professional package insert and final printed carton and container labels. This labeling is in accordance with agreements made in our discussions with the firm. The patient package insert has been submitted in draft. Any further changes that we recommend can be incorporated into the draft and conveyed to the applicant in the approval letter.

The application will be approved on the final printed professional package insert, final printed carton and container labels, and a draft patient package insert.

2) The applicant was asked to meet with the Agency so that a decision could be made regarding their proposed marketing and distribution plan.

Resolution: This issue was addressed in our labeling discussions. Information on their marketing and distribution plan was incorporated into the labeling. In discussions with the firm prior to approval, it was suggested that we might approve this application under subpart H. Dr. Temple decided that this would not be necessary (see Office Director's memorandum).

3) Interim dissolution specifications and method were proposed in the approvable letter.

Resolution: We met with the applicant on April 7, 1999, and an agreement was made regarding interim dissolution specifications and method. The firm also agreed to conduct phase 4 studies to determine the final dissolution methods and specifications. This commitment was made in writing in their submission of September 8, 1999.

4) The approvable letter did not address the need for pediatric studies, but since the 1998 Pediatric Rule became effective on April 1, 1999, that issue must now be addressed.

Resolution: The requirement for pediatric studies will be deferred for a period of two years until more data can be obtained regarding the safety and effectiveness of dofetilide in adults.

/S/ 9-15-99

David Roeder
Regulatory Health Project Manager

cc: NDA 20-931
HFD-110
HFD-110/DRoeder

RHPM Review Package Overview

Application: NDA 20-931
Tikosyn (dofetilide) Capsules
125, 250 and 500 mcg

Applicant: Pfizer Pharmaceutical Production Corporation Limited
U.S. Agent: Pfizer Inc.

Submission Date: March 9, 1998

User Fee Date: March 9, 1999

Priority: 1P

Chemistry

Reviewer: Stuart Zimmerman, Ph.D.

Review dates: January 26, 1999
February 10, 1999

The reviewer recommends approval **pending completion of the inspection of the applicant's Puerto Rico facility**.

The Labeling and Nomenclature Committee has found the tradename to be acceptable.

Pharmacology

Reviewer: Pritam Gill-Kumar, M.D.

Review date: January 6, 1999
February 10, 1999

CAC review is complete and all issues have been resolved. The reviewer's comments have been incorporated into the labeling.

Clinical Pharmacology/Biopharmaceutics

Reviewer: Emmanuel Fadiran, Ph.D.

Review date: December 10, 1999

The reviewer's comments have been incorporated into the package insert. Dissolutions issues can be addressed after approval.

Clinical /Statistical

Medical Reviewers: Knud Knudsen, M.D., (clinical pharmacology) 12-15-98
Maryann Gordon, M.D. (safety and clinical pharmacology) 12-15-98 and 1-22-99
Akinwole Williams, M.D. (safety/DIAMOND) 12-29-98
Charles Ganley, M.D. (efficacy)

Statistical Reviewers: Lu Cui, Ph.D. (DIAMOND) 12-29-98

James Hung, Ph.D. (efficacy)

All medical and statistical issues have been addressed by the secondary reviewer.

Safety Update

The 4-month safety update is reviewed in Dr. Gordon's safety review. A final safety update is not necessary

DSI

All DSI audits are complete. No significant problems were identified.

Secondary Review

Reviewer: Shaw Chen, M.D., Ph.D.

Date of Review: January 26, 1999

Dr. Chen recommends approval for conversion and maintenance of chronic AF/AFl in patients with left ventricular dysfunction. A less restrictive claim would require a head-to-head comparison with currently approved therapies.

/S/

David Roeder
Regulatory Health Project Manager

dr/2-1-99/2-12-99

13. PATENT AND EXCLUSIVITY INFORMATION FOR DOFETILIDE

1.	Active Ingredient:	*N*-[4-(2-{2-[4-(methanesulphonamido) phenoxy]-*N*-methylethylamino}ethyl) phenyl]methanesulphonamide
2.	Strengths:	0.125 mg (125 mcg), 0.25 mg (250 mcg), 0.5 mg (500 mcg)
3.	Trade Name:	TIKOSYN
4.	Dosage Form/Route of Administration:	Capsules / Oral
5.	Applicant Firm Name:	Pfizer Pharmaceuticals Production Corporation Limited Ringaskiddy County Cork, Ireland
6.	NDA Number:	20-931
7.	Exclusivity Period:	5 years from the date of approval of this application, as provided in FDCA Section 505(j)(4)(D)(ii)
8.	Applicable Patent Numbers and Expiration Dates:	4,959,366 September 25, 2007

14. PATENT CERTIFICATION

With respect to the drug, TIKOSYN, which is the subject of this Application (NDA- #20,931) and the U.S. patent(s) which are listed in Section 13 of this NDA, Pfizer certifies that the drug, TIKOSYN, and formulations and uses thereof are claimed by U.S. Patent No. 4,959,366.

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20931	**Trade Name:**	TIKOSYN ~~DOFETILIDE~~ ORAL CAPS
Supplement Number:		**Generic Name:**	DOFETILIDE ORAL CAPS
Supplement Type:		**Dosage Form:**	Capsule; Oral
Regulatory Action:	PN	**Proposed Indication:**	Conversion and maintenance of atrial fibrillation and flutter

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No data was submitted for this indication, however, plans or ongoing studies exist for pediatric patients

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
Currently deferred until further efficacy and safety data are obtained, at which time, a decision will be made as to whether studies are necessary.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, DAVID ROEDER

/S/ 9-15-99

Signature Date