CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20931

ADMINISTRATIVE DOCUMENTS

D. Loeder

MAR 2 - 1999

NDA 20-931 Tikosyn Capsules (dofetilide capsules, Pfizer)

PHARMACOLOGY TEAM LEADER'S REVIEW OF LABELING

This document is directed at only the PRECAUTIONS section of the product labeling and considers only those subsections for which statements are based on the results of animal investigations.

Changes Recommended by the Primary Reviewer

The rationale supporting these changes is provided on pages 9 and 10 of Dr. Gill Kumar's review. Note that Dr. Gill-Kumar's proposed additions to the sponsor's proposed wording are double underlined and that an entirely new section, "Testicular Effects Seen in Subchronic & Chronic Animal Studies", has been proposed.

Team Leader Recommendations

Changes to the primary reviewer's suggested text are recommended:

These changes, as well as (minor) changes to the format and syntax of the (primary reviewer's proposed) labeling, are outlined below.

Under **Carcinogenesis, Mutagenesis, Impairment of Fertility**, replace the last two sentences of Dr. Gill-Kumar's first paragraph (The AUC.....in the clinical setting.) with the following sentence:

The proposed new section on testicular effects in animals should be incorporated into the second paragraph under **Carcinogenesis, Mutagenesis, Impairment of Fertility**. That paragraph should now read as follows:

Under **Pregnancy Category C**, the text should be replaced with the following:

Note that this team leader review deals only with the PRECAUTIONS section of the package insert. The primary reviewer's recommendations for other sections of the package insert are accepted without comment.

/S/

Charles A. Resnick, Ph.D.
Division of CardioRenal Drug Products
Friday, January 15, 1999

cc:
NDA 20-931
HFD-110
HFD-110/CSO
HFD-110/PGill-Kumar
HFD-110/CResnick

msword\tikosyn.lab.doc

912 MAR 5 1998

REQUEST FOR TRADEMARK REVIEW

TO: CDER Labeling and Nomenclature Committee
Attention: Dan Boring, R.Ph., Ph.D. HFD-530
9201 Corporate Blvd. Rm N 461

FROM: Division of: Cardio-Renal Drug Products HFD-110
Attention: Robert Wolters Phone: 594-5376

DATE: December 3, 1997

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Proprietary Name: Xelide NDA/ANDA NDA 20-931

Trademark status: Yes No Pending

Company Name: Pfizer

Other proprietary names by the same firm for companion products:
None

Established name including dosage form and strength: Capsules 0.125, 0.25 & 0.5 mg Capsules
Dofetilide

Indications for use including dosing schedule (may be a summary if proposed statement is lengthy):
Atrial fibrillation/flutter & life-threatening ventricular arrhythmia
Class III antiarrhythmic agent.

Comments from the submitter: (concerns, observations, etc.)
This trademark was sent to the committee in January for consideration under the IND

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. Dec.96

Consult #912 (HFD-110)

XELIDE dofetilide capsules

This is a re-consult from an earlier IND submission. The committee found no new reasons to find the name unacceptable.

The Committee has no reason to find the proposed proprietary name unacceptable.

/S/ 2/24/98, Chair
CDER Labeling and Nomenclature Committee

FEB 25 1998

903

REQUEST FOR TRADEMARK REVIEW

TO: CDER Labeling and Nomenclature Committee
Attention: Dan Boring, R.Ph., Ph.D. HFD-530
9201 Corporate Blvd. Rm N 461

FROM: Division of: Cardio-Renal Drug Products HFD-110
Attention: Robert Wolters Phone: 594-5376

DATE: November 3, 1997

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Proprietary Name: Restosyn NDA/ANDA IND

Trademark status: Pending

Company Name: Pfizer Central Research

Other proprietary names by the same firm for companion products:

Established name including dosage form and strength: Dofetilide capsules 0.125 mg, 0.25 mg & 0.5 mg. They had originally proposed an injectable drug product, but decided to submit a NDA only for the capsules.

Indications for use including dosing schedule (may be a summary if proposed statement is lengthy):
Selective potassium channel blocker for the treatment of cardiac arrhythmias.

Comments from the submitter: (concerns, observations, etc.)

Alternative trademarks Tikosyn, Allsync and Enablex

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. Dec,96

Consult #903 (HFD-110)

RESTOSYN
ENABLEX
ALLSYNC
TIKOSYN dofetilide hydrochloride

The Committee noted one sound-alike/look-alike conflicts with the following marketed product: RESTORIL. The committee felt there was a low potential for mix-up with these products since they differ in strengths available and therapeutic class. However, the committee felt that the name communicated "restores synchronicity" and was viewed as a fanciful statement. Similarly, the names ENABLEX and ALLSYNC were evaluated as being unduly fanciful.

The Committee noted sound-alike/look-alike conflicts between TIKOSYN and the marketed product, TICLID and USAN, teclosin. The committee felt there was a low potential for mix-up with these products since they differ in strengths available and therapeutic class. There were no misleading aspects found.

Overall the committee found RESTOSYN, ENABLEX and ALLSYNC unacceptable, but has no reason to find TIKOSYN unacceptable.

/S/ 7/23/98, Chair
CDER Labeling and Nomenclature Committee

Reader

AUG 1 1 1998

Executive CAC
Date of Meeting: August 11, 1998
Members of ExecCAC in Attendance:
Dr. Osterberg
Dr. Contrera
Dr. DeGeorge
Dr. Resnick

Note on additional information supplied on IND (NDA 20-931)

Dr. P. Gill-Kumar provided the Exec CAC with a draft review addressing the unanswered issues from the May 26th meeting on IND

The NDA contained preclinical exposure data for both the rat and mouse, cross species comparisons of protein binding, and comparative metabolism data not presented at the original meeting of the Exec CAC. It is clear from the data provided that the comparison of parent drug AUCs underestimates the relative systemic exposure across species to drug and metabolites that appear in all species (although at different ratios) and that using AUCs uncorrected for protein binding also underestimates relative exposure. It is the committee members' consensus that the necessary exposure multiple defined by the ICH guidance document had been exceeded when applying appropriate evaluation criteria for both the mouse and the rat. Dose selection for both carcinogenicity studies was thus concluded as adequate.

The issue of the biological significance of the ganglioneuroma was also addressed. It was determined that this tumor should be evaluated by combination from all sites. As such it was no longer viewed as a rare tumor, and thus, it was no longer viewed as a significant finding. This view of Dr.Gill-Kumar was supported by the committee.

Dr. P. Gill-Kumar's view that one should only correct for protein binding when it decreases the ratio of exposure between animals and humans is <u>not</u> in accord with Center or International policy, guidance, or practice, or with reasonable scientific principles.

8/26/98

/S/
Joseph DeGeorge
Chair, ExecCAC

CC: IND
NDA 20,931
HFD-110
HFD-110/DReeder

D. Rueda

From: P. Gill-Kumar
To: Executive CAC
Through: Dr. C. Resnick

AUG 7 1998

Ref the recommendations made by the CAC regarding the carcinogenicity studies conducted under IND # [redacted] at the CAC meeting held on May 26, 1998, the following report is being submitted.

Metabolism of dofetilide in man, rat (SD, male & female), and mouse (CD-1, male):

Table 1 shows % of administered radioactivity excreted in urine and feces after oral administration of [^{14}C]-dofetilide in man, rat, and mouse (in the mouse, it seems that pooled urine and feces were examined). Table 2 shows dofetilide and various metabolites excreted in urine in 24 hours (as % of radioactivity excreted in urine, and in ( ) as % of the administered dose) in these species.

Table 1

Species	Dose (oral)	% excreted in urine		% excreted in feces		Total recovered
		24 hours	120 hours	48 hours	96 hours	
Man (n=3)	0.5 mg	66.8±4.8	77.6±3.1	6.5±6.7	10.13±4	87.7 %
Rat (m) (n=3)	5 mg/kg	43.1±3.4	47.7±2.9	48±2	48.5±2	96.2%
Rat (f) (n=3)	7 mg/kg	52.8±3.8	54.4±4.1	41±4.7	41.4	95.8%
Mouse (n=4)	4.4 mg/kg	54.5	56.8	37.1	38.3	95.1%

Table 2

Species	Dofetilide	UK-80,725	UK-69,502	UK-71,385	UK-116,856	M2	Total
Man (n=3)	82.9±2.5 (64.4)	3.3±1.3 (2.3)	1.32±0.6 (1.01)	2.9±0.8 (2.3)	3.2±0.4 (2.5)	-	93.6
Rat (m) (n=3)	20 (9.5)	32 (15.3)	19 (9.1)	21 (10)		-	92
Rat (f) (n=3)	38 (20.7)	28 (15.2)	15 (8.2)	12 (6.5)		-	93
Mouse (n=4)	21 (11.4)	23 (12.5)	8 (4.4)	27 (14.7)		18 (9.8)	97

In man, dofetilide constituted ≈71% of [^{14}C] AUC; plasma levels of metabolites were not determinable. (In rat and mouse, [^{14}C] AUC is not in the data base provided). Dofetilide is much more extensibly metabolized in rodents than in man.

Discussion: There is only one metabolite (UK-116,856) which is present in man, but has not been identified in rat and mouse, but <3% of the administered dose seems to be converted to this metabolite in 24 hours. Since plasma levels of all metabolites in man were below detection limits, and metabolism of dofetilide in rat and mouse is more extensive than in man, dofetilide AUC can be used to assess the adequacy of the rodent carcinogenicity studies.

Rat carcinogenicity study:

- Adequacy issue:

After the CAC meeting, I found a toxicokinetic study (#[redacted] in which 5, 10, and 50 mg/kg/day dofetilide were administered as dietary mix to 3 groups of male rats ([redacted] COBS-VAF-CD (SD) BR; n=10/group). After 2½ months, plasma levels of dofetilide were determined; plasma from each subgroup of 5 rats was sampled at 8 hourly intervals, sampling in the two subgroups being staggered by 4 hours. At 10 mg/kg/day dose, C_{max} was 155±48 ng/ml (mean ± sd), and mean $AUC_{0\text{-}24h}$ was 1950 ng*h/ml. In the gavage study that was presented at the CAC meeting, AUC in female rats was not < than that in males. Therefore, it seems reasonable to assume that AUC

in the high-dose female rats in the carcinogenicity study would not be < AUC in males.

Mean AUC in the human pharmacokinetic study (protocol 115-229, in IND Ssn N(RD)171) was 51 ng*h/ml. The mean AUCs in high dose animals in the carcinogenicity study would be ≈38 times this value.

In the dofetilide NDA, there are several human pharmacokinetic studies. In 10/13 studies (n=18-20 in each) AUC was 41-48 ng*h/ml; in 4, it was 50-55 ng*h/ml; and in one (protocol, 115-211;n=12), mean AUC was 61 ng*h/ml; several individual subjects of course would have values higher than the mean, but 95% subjects would have AUCs ≤ 'mean+1.6*sd'. Mean+1sd value of AUC in protocol 15-211 is ≈ 75 ng*h/ml. Mean AUC in the high dose groups in the carcinogenicity study is 26 times this value.

Therefore, based on the agency's criterion of an AUC ≥ 25 times the maximum likely human AUC, high dose in the rat carcinogenicity study was adequate.

- Incidence of ganglioneuroma: When the carcinogenicity study was presented to the CAC, the table listing tumors that were numerically increased in any treatment group, listed the incidence of ganglioneuroma in the pituitary, which was 1/48 and 1/50 respectively in the male and female high dose groups. However, this is a tumor, for which incidences at all sites should be combined. This tumor was found in the pituitary and thyroid; when all sites are considered together, the incidences are as shown in the table below.

	C1	C2	L	M	H
Males	2/49	0/48	0/45	0/46	3/48
Females	0/49	1/48	1/46	0/50	1/50

Therefore, the issue of this being a very rare tumor for which even a very low statistically non-significant incidence may be matter of concern, is not an issue any more.

Mouse carcinogenicity study:

- Adequacy issue:

In the dietary pharmacokinetic study, mean AUC (males +females combined) was 724 ng*h/ml, and plasma protein binding was 46-48%. Using the higher figure, 52% dofetilide would be free, and AUC of the free component would be 376 ng*h /ml. In man, plasma protein binding at 10 ng/ml drug concentration was 68% (C_{max} in man is ≈ 4 ng/ml); mean AUC of free drug in protocol 115-229 would be ≈16 ng*h/ml. Mean AUC of free dofetilide in the mouse would be *23 times this value*. 'Mean +1.6*sd' of free dofetilide AUC in protocol 115-211=24 ng*h/ml; AUC of free dofetilide in the mouse is *16 times this value.* As discussed in the rat study, the latter value in man in my opinion is the more appropriate value to use for comparison.

There is an additional issue in using this pharmacokinetic study for assessing the adequacy of the carcinogenicity study. In this study, AUC was calculated using mean plasma levels of 3m+3f, and a different group of animals was used for each time point. Taken separately, AUC in males was 927 ng*h/ml, in females 560 ng*h/ml, and free dofetilide AUCs in males and females would be 482 ng*h/ml and 291 ng*h/ml respectively.

However, since the number of animals sampled at each time point is only 3/sex, it is not possible to draw any inference regarding the similarity or otherwise of male and female AUCs in the mouse.

There are no other mouse pharmacokinetic studies in the NDA, from which an assessment could be made as to whether combining males and females in the study referred to above is appropriate.

Therefore, in my opinion there is no valid data based on which the adequacy of the mouse carcinogenicity study in terms of AUC can be assessed. We had requested the sponsor to perform a dietary pharmacokinetic study in the mouse, using at least 5 animals/sex/sampling point and calculate AUCs for males and females, but the sponsor did not seem willing to do so.

Comments regarding use of AUC of the free component:

I am presenting here my opinion on this issue and the basis for that opinion. In assessing the adequacy of any toxicity study and the likely implications of adverse findings for patients, one should err on the side of safety. If drug AUC is used for assessing the adequacy of carcinogenicity studies, of course it is important to determine that protein binding is not greater than in man. If it is, one should then use free AUC. However, if protein binding is smaller than in man, one should not then go on to determine if AUC of free drug meets the criterion of magnitude. This is because pharmacokinetic studies in animals are done using only 3-5 animals, and often different sets of animals (of necessity) are used at different time points. AUC , consequently is a very rough estimate. Erring on the side of safety therefore requires that AUC of free component not be used in the case where protein binding is < than in man.

/S/

Pritam Gill-Kumar, M.D.
Aug 6, 1998

cc: HFD 110/Original IND
HFD/CSO
HFD 110/C. Resnick

D. Roeder

JUN 24 1998

Minutes of a Telecon between Pfizer and the FDA

Date: June 12, 1998

Application: NDA 20-931
Tikosyn (dofetilide) Capsules

Applicant: Pfizer

Subject: CAC Recommendations

Participants:

FDA

Charles Resnick, Ph.D., HFD-110, Pharmacology Team Leader
Pritam Gull-Kumar, M.D., HFD-110, Pharmacologist
David Roeder, HFD-110, Regulatory Health Project Manager

Pfizer

Dr. Bill Murphy, Regulatory Affairs
Dr. Chris Peters, Toxicology
Dr. Peter Graepel, Toxicology
Dr. Claude Charuel, Toxicology

Background

The CDER executive carcinogenicity assessment committee (CAC) met on May 26, 1998 to review NDA 20-931. They recommended that the sponsor conduct a dietary pharmacokinetics (PK) study in rats to support the adequacy of the carcinogenicity study in that species. The recommendation was based on the presentation of the primary reviewer, Dr. Gill-Kumar, who was, at that time, unaware that a dietary PK study had already been performed in (male) rats. Nonetheless, a tentative decision to convey the CAC recommendation to the sponsor was made by the team leader, Dr. Resnick, since there was still an absence of information on PK following dietary administration to female rats. The primary reviewer and team leader also felt that it would be worthwhile to repeat the dietary PK study that had been performed in mice since the number of animals studied was insufficient to assess gender differences. When the project manager, Ms. Diana Willard, called the sponsor to advise them that a letter recommending that these studies be performed would be forthcoming, the sponsor asked to discuss the need for such studies prior to our issuing the letter.

Telecon

Rat Study

Dr. Gill-Kumar pointed out the concerns of the division (noted above). The sponsor pointed out that their gavage study in male and female rats showed no difference between the sexes. Dr. Gill-Kumar agreed to review that study again to determine if the data support the sponsor's conclusion. Dr. Resnick agreed with the sponsor that a finding of no difference between the sexes would obviate the need for another dietary administration study.

Regarding the need for another PK study in the mouse, Dr. Gill-Kumar noted that the sponsor would not be asked for another study without an endorsement of that recommendation by the CAC.

Conclusion

Dr. Resnick asked the firm to present their arguments in a written submission. We will get back to them after reviewing their arguments and conferring with the CAC.

Minutes preparation: /S/
David Roeder

Concurrence Chair: /S/
Charles Resnick, Ph.D.

dr/6-18-98/6-25-98

RD: PGill-Kumar/6-18-98
CResnick/6-22-98

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

110 file

JUN 10 1998

D. Reeder

Executive CAC
Date of Meeting: May 26, 1998

Committee:
Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-900, Member
Andrea Weir, Ph.D., Alternate Member
Charles Resnick Ph.D., Team Leader
Pritam Gill-Kumar, M.D. , Presenting Reviewer

Author of Draft: P. Gill-Kumar

The following information reflects a brief summary of the Committee discussion and its recommendations.
Detailed study information can be found in the individual review.

IND
Drug Name Dofetilide
Sponsor: Pfizer Central Research

Mouse Carcinogenicity Study

There was no treatment related adverse effect on survival, and the drug was not tumorogenic. The issue is adequacy of dosing. There is a pharmacokinetic mouse study in the NDA (# 20, 931) in which the highest dose in the carcinogenicity study was administered for 25 days as a dietary mix. The AUC in this study was 14 times the mean AUC in man at the highest proposed dose. Plasma protein binding in mouse is 46-48% which is not > than plasma protein binding in man (64%).

Dr. DeGeorge said that AUC in the mouse should be adjusted for a lower protein binding compared to man, before deciding whether the AUC in mouse meets the agency's criteria. He also said that the division should get information about drug metabolism in man and mouse from the NDA to help in making a determination about the adequacy of the mouse study

Dr. Gill-Kumar said that this would not be appropriate, since the mouse pharmacokinetic study (like most such studies) is crude; different animals are used for blood sampling at different time points, and the number of animals /per time point is small.

Rat Carcinogenicity Study

There was no treatment related adverse effect on mortality, and the drug was not tumorogenic. There is a gavage study in the rat; using an estimated AUC from this study (by interpolation) and using the factor of 0.74 (from dietary and gavage studies in the mouse, assuming that the effect of diet on bioavailability of drug in the rat is similar to that in the mouse) to adjust for the effect of diet, estimated AUC in the male and female rats is 22 and 28 times respectively the maximum AUC in man. The issue is adequacy of dosage; whether the estimates are acceptable to the CAC in lieu of a dietary pharmacokinetic study,

Dr. DeGeorge said: 1) Determination of adequacy cannot be made without data from a dietary pharmacokinetic study in the rat, and the sponsor should be asked to do such a study. 2) Regarding tumorogenic effects, ganglioneuroma was found in 1 high dose animal in both males and females, and none of the control groups had this tumor. The division should find out the incidence of this tumor in control animals in the testing lab.

Executive CAC Recommendations and Conclusions:

Rat:

- Sponsor should be asked to conduct a dietary pharmacokinetic study for supporting the adequacy of the Carcinogenicity study.
- Division should get information about the incidence of pituitary ganglioneuromas in control animals in the testing lab.

Mouse:

- Division should: 1) Evaluate information about drug metabolism in mouse and man from the NDA , and 2) Recalculate AUC ratios for mouse and man, using respective protein binding in the two species. This information should be sent to Ms Adele Seifried for forwarding to CA members.

/S/ for /S/ 6/5/98

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:\
/Division File, HFD 110
/CResnick, HFD-110
/PGill-Kumar, HFD-110
/ASeifried, HFD-024

D. Willard

MAY 14 1998

Minutes of a Teleconference
May 14, 1998

Application: NDA 20-931
Tikosyn (dofetilide) Capsules, 0.125, 0.25, and 0.5 mg

Sponsor: Pfizer Pharmaceuticals Corporation Limited

Purpose of Telecon: Clarify Division requests for information

Attending:

Pfizer:

Dr. B. Marchant	Clinician
Mr. G. Andrews	Data Team Leader, Biometrics
Mr. D. Evans	Information Systems Group
Mr. J. Salkeid	Information Systems Group
Mr. Charles Kent	
Dr. William Murphy	Associate Director, Regulatory Affairs

FDA:

Akinwole Williams, M.D.	Medical Officer, HFD-110
Lu Cui, Ph.D.	Biostatistician, HFD-713
Diana Willard	Regulatory Health Project Manager, HFD-110

Meeting Chair: Akinwole Williams, M.D.

Meeting Recorder: Diana Willard

Background: This meeting was requested by the Division to clarify several requests for information that had been made by Dr. Williams and Dr. Cui and to establish a timeline for when Pfizer would provide the requested information.

Teleconference:

Dr. Williams began by stating that there are three pieces of information that have been requested:

- the SAS data files containing the last clinic date for each surviving DIAMOND patient,
- the duration of follow-up of each patient,
- and the date when each patient stopped therapy. It was noted that this date is difficult to determine from the information provided because there are multiple dates for each patient.

Dr. Williams further requested information concerning the methodology of the randomization for patients in the DIAMOND study. How were these patients randomized: Was it consecutive randomization? How did the investigators in each center randomize their patients?

In response to Dr. Williams, Dr. Marchant clarified that there were different follow-up periods for different endpoints in DIAMOND. Deaths in DIAMOND were followed to the close of the study on December 10, 1996. The other study endpoints in DIAMOND were followed for three months. Dr. Williams stated that it is necessary to establish the duration of therapy for each patient. Pfizer stated that Dr. Williams would be provided with information concerning the duration of follow-up from randomization to the last clinic date.

Pfizer will establish a timeline for responding to Dr. Williams queries and then contact Ms. Willard to provide dates for delivery of the requested datasets.

Dr. Cui questioned Pfizer regarding the hypothesis being tested in the DIAMOND studies. Was the DIAMOND null hypothesis that dofetilide was not better than placebo? Pfizer responded that the studies were prepared to accept that dofetilide could result in either an increase or decrease in mortality. Regarding the boundaries for stopping the trial, Dr. Cui wanted to know how the interim analyses were performed for the DSMB, including the timing for the interim analyses and the outcome of each interim analysis. Specifically, Dr. Cui requested to know what information was provided to the DSMB and the decisions reached based on that information. Pfizer stated that the information provided to the DSMB at the interim analyses would be provided along with a summary table explaining the DSMB decisions.

Signature, Minutes Preparer /S/ Diana Willard

Concurrence, Meeting Chair /S/ Akinwole Williams, M.D.

cc: original file
HFD-110
HFD-110/DWillard
HFD-110/SBenton

Drafted: 6/10/98
RD: Williams 6/25/98
Cui 6/26/98

D. Willard

MAY 22 1998

Minutes of a Teleconference
April 14, 1998

Application: NDA 20-931
Tikosyn (dofetilide) Capsules, 0.125, 0.25, and 0.5 mg

Sponsor: Pfizer Pharmaceuticals Corporation Limited

Purpose of Telecon: Discussion of proposed dosing regimen/safety data in NDA

Attending:

Pfizer:

Bradley Marchant, M.D.	Clinician
Carol Statler, M.D.	Clinician
Paul Nitschman, M.D.	Dofetilide Safety
Don Nichols, Ph.D.	Clinical Pharmacology
Don Evans, Ph.D.	Biometrics
William Murphy, Ph.D.	Associate Director, Regulatory Affairs

FDA:

Shaw Chen, M.D., Ph.D.	Team Leader/Medical, HFD-110
Charles Ganley, M.D.	Team Leader/Medical, HFD-110
Maryann Gordon, M.D.	Medical Officer, HFD-110
Diana Willard	Regulatory Health Project Manager, HFD-110

Meeting Chair: Shaw Chen, M.D., Ph.D.

Meeting Recorder: Diana Willard

Background: This teleconference was scheduled to discuss the proposed dosing regimen for Tikosyn as well as the safety data submitted in the NDA to support that regimen.

Teleconference: Dr. Gordon stated that there is a need to discuss the difference between the actual dose the patient was on at the end of a study as opposed to the randomized dose. It was noted that all safety tables are based on the randomized dose and that patients were frequently down-titrated; 500 mg BID was the randomized dose in most studies and patients could be down-titrated for QT_c prolongation or for low creatinine clearance.

Pfizer stated that their key concern throughout the dofetilide development program was to limit any increase in QT_c from baseline. Patients with an increase from baseline QT_c were taken off drug. From the dofetilide pK studies, it is known that patient exposure to drug is dependent on creatinine clearance. In an effort to reduce high end QT, dose was adjusted according to creatinine clearance. The proposed labeling reflects how dose adjustments were made in the majority of Phase III studies.

Pfizer noted that in the majority of dofetilide protocols, a minimum hospital stay of two and a

half days was required. During that two and a half days, dose adjustment was possible. At discharge, the patient went home on a maintenance dose. In long-term studies, however, dose adjustment could have occurred both during hospitalization and during the maintenance period if creatinine clearance measurements were low.

Dr. Gordon noted that, at discharge, in Diamond CHF, only 27% of the patients were on 500 mg BID. Pfizer said in Diamond CHF, 25% of the patients enrolled had atrial fibrillation at baseline and so received 250 mg BID. The remaining 75% of the patients were randomized to 500 mg BID. Of that 75%, approximately 50% had renal impairment and were down-titrated to 250 mg BID.

Dr. Ganley emphasized that if the majority of patients were not receiving 500 mg BID at the time the studies ended, a question arises regarding the validity of the safety data provided in the NDA. The could also potentially affect the mortality claim.

Pfizer emphasized that they are claiming that the proposed dosing regimen follows a scheme based on patient response; the patient will be down-titrated for QT_c prolongation or low creatinine clearance. Pfizer added that there is limited data available from dofetilide studies where the protocol did not allow a reduction in dose. It was noted that the results of the ISE are compatible with the ISS.

The Division stated that safety data based on the actual dose taken should be provided. Pfizer cautioned that such safety data would provide information that is from a "mixed bag" of patients; those receiving 500 mg BID as well as those down-titrated.

It was noted that, for the pivotal trials, no information is available to explain why the hospital physician decreased the dose.

The Division requested safety data for the following four patient groups:

- 500 mg BID (not down-titrated)
- down-titrated for renal function (low creatinine clearance)
- down-titrated for other reasons
- randomized to 250 mg BID

If efficacy data are needed for these four groups, it will be requested at a later date. Pfizer noted that a number of the patients randomized to 250 mg BID were down-titrated to 125 mg BID.

Dr. Gordon requested that only the studies targeted to support the SVT claim, i.e., the studies utilized for Dr. Pritchett's analysis, be submitted in the revised safety tables. The safety tables should first list pro-arrhythmias, then adverse events, then discontinuation by dose, etc. Pfizer will provide for Division review a draft table as well as a timeline of when the information will be available.

The Division noted that the filing meeting for Tikosyn will be held April 15, 1998. The issues raised during this teleconference will be discussed with Dr. Lipicky at that time. If other concerns arise during the filing meeting, Pfizer will be notified.
Dr. Ganley requested that the dates of protocols and amendments submitted to the IND for pivotal and primary supporting studies be provided. He stated that he has found it difficult to use the

hard copy of the NDA as there is no index in a number of the volumes. This makes it difficult to locate graphs and tables in the hard copy.

Signature, Minutes Preparer /S/ Diana Willard

Concurrence, Meeting Chair /S/ Shaw Chen, M.D., Ph.D.

cc: original file
HFD-110
HFD-110/DWillard
HFD-110/SBenton

Drafted: 4/28/98
RD: Chen 4/29/98
Ganley 4/29/98
Gordon 5/7/98

MAR 16 1999

Minutes of a Telephone Conference Call Between Pfizer Inc. and the FDA

Date of Meeting: March 4, 1999

Application: NDA 20-931
Tikosyn (dofetilide) Capsules

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

Subject: Pharmacology/Toxicology

Participants:

FDA

Charles Resnick, Ph.D., HFD-110, Pharmacology Team Leader
Pritam Gill-Kumar, M.D., HFD-110, Pharmacologist
David Roeder, HFD-110, Regulatory Health Project Manager

Pfizer

Dr. William Murphy, Regulatory Affairs
Dr. Chris Peters, Toxicology

Background
This telephone conference call was scheduled to discuss the FDA's determination of the no-effect dose of dofetilide in the dog.

Telecon

Dr. Gill-Kumar noted that in the one year study, animal #23 in the 1 mg/kg group had multifocal bilateral testicular atrophy. Multifocal atrophy was not seen in any of the animals in either the low dose (0.1 mg/kg.day) group or the control group.

The sponsor argued that the histological findings in the testes might be due to sexual immaturity of the animals. Dr. Gill-Kumar noted, however, that multifocal testicular atrophy was not observed in any of the 12 dogs in the one month study (these dogs would have been the most sexually immature of all animals in various studies) and in any of the 16 low dose and control animals in the six and 12 month studies. Therefore, the lesions seen in animal #23 in the one year study are unlikely to be due to sexual immaturity, and 0.1 mg/kg/gay is the No Observed Adverse Effect Dose (NOAED).

Minutes Preparation: /S/
David Roeder

Concurrence Chair: /S/
Charles Resnick, Ph.D.

dr/3-11-99/3-16-99

RD: PGill-Kumar/3-12-99
CResnick/3-12-99

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

Memorandum to the File

Application: NDA 20-931
Tykosin (dofetilide) Capsules

APR - 1 1999

Applicant: Pfizer

Subject: Labeling

Dofetilide will be supplied in the following strengths: 0.25 mg (250 mcg) and 0.5 mg (500 mcg). The labeling in the approvable letter used "mg" as the primary unit of measure when referring to the dosage strengths. After some internal discussions, the Agency decided that, for safety reasons, the primary unit of measure should be "mcg." Our concern was that 0.25 mg or 0.5 mg could be misread if the "0' is omitted or if the decimal is not clear. We would expect fewer medication errors with the use of 250 mcg and 500 mcg.

I called Bill Murphy on March 16, 1999, and asked that they revise the labeling so that the dosage strength be referred to in mcg when only one unit of measure is used. When mcg and mg are both used, "mcg" should precede "mg," and "mg" should be in parenthesis, as follows: 250 mcg (0.25 mg) and 500 mcg (0.5 mg).

/S/

David Roeder
Regulatory Health Project Manager

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

JUL -2 1999

Minutes of a Telephone Conference Call Between Pfizer and the FDA

Date of Telecon: June 21, 1999

Application: NDA 20-931
Tikosyn (dofetilide) Capsules

Sponsor: Pfizer Pharmaceutical Production Corporation Limited
U.S. Representative: Pfizer Inc.

Subject: Labeling

Participants:

FDA

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation I
Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Shaw Chen, M.D., Ph.D., HFD-110, Medical Group Leader
Maryann Gordon, M.D., HFD-110, Medical Officer
David Roeder, HFD-110, Regulatory Health Project Manager

Pfizer

Rita Wittich, Regulatory Affairs
Inna Kissen, Ph.D., Regulatory Affairs
Paul Nitschmann, M.D., Regulatory Affairs
Cheryl Graham, M.D., Regulatory Affairs
Tilman Friedrich, M.D., Medical
Bradley Marchant, M.D., Medical
Barbara LePetri, M.D., Medical
Bill Murphy, Ph.D., Regulatory Affairs

Background

Pfizer responded to the March 5, 1999 approvable letter for NDA 20-931 with a submission of draft labeling dated April 28, 1999. The FDA responded to that submission with a marked-up draft faxed on June 15, 1999. Dr. Temple asked for a telephone conference with the sponsor to discuss the possibility of including an alternate approach to dosing in the package insert.

Telephone Conference

Alternate Dosing

The current draft labeling for dofetilide recommends dosing patients at the highest tolerated dose based on creatinine clearance and QTc. Dr. Lipicky pointed out that since there are dose-related pro-arrhythmic effects of dofetilide, and dofetilide would be used for symptomatic treatment, it might be prudent to begin treatment at lower doses, as these too have been shown to delay reccurrence of AF. He believed that some patients would achieve control (delay) of recurrence on the lower doses that they would consider adequate, even if their creatinine clearance and QTc would allow them to have received 500 mg. The ones that recurred too quickly could be given the higher dose next time. Patients would have to receive the highest dose for conversion to sinus rhythm in the hospital because lower doses were not effective in that setting. He believed that such an approach would give the physician more flexibility in risk management.

Dr. Temple asked that the sponsor consider including this dosing approach as an alternative to (not a replacement for) the approach used in the clinical trials. He noted that the effectiveness of the 125 mg dose was variable, and it might be reasonable to consider only the 250 mg dose.

The sponsor was concerned that such an addition to the labeling would make the package insert too complicated. They noted also that if patients were given a lower dose after leaving the hospital, they would be more likely to recur and would have to be re-hospitalized for cardioversion and retreatment.

Dr. Temple agreed that was so but thought some patients would accept that trade-off. He suggested that the sponsor might be able to craft a not too complicated statement to add to the **DOSAGE AND ADMINISTRATION** section that would give the patient and physician the option use a lower maintenance dose. He believed that it would be worth trying such an approach, but said the decision was up to the sponsor and that we were no wedded to it. Pfizer agreed to explore the issue. If they decide to try it, they will submit revised labeling.

Unit of Use Dosing

The sponsor asked for clarification of the Agency's request that they supply dofetilide in Unit of Use packaging only. They plan to supply it initially in bottles with a 1-week and 1-month supply. At a later date, they will market a 3-month supply bottle. Dr. Temple responded that his concern was not with the bottle size, but rather that all bottles contain the patient package insert.

Black Box Warning

The Agency had recommended that the dofetilide package insert contain a black box Warning. Pfizer representatives were concerned that this would prohibit them from distributing "reminder" advertisements that they believe would help patients remember to take their dofetilide regularly. Dr. Temple said that a black box Warning is necessary for drugs such as dofetilide that are associated with a preventable lethality. He suggested that the sponsor make a proposal for a waiver that would allow them to distribute reminder adds that are geared towards enhancing patient compliance.

Patient Package Insert

Dr. Temple had asked that the patient package insert be written in the format of the Medication Guide. Dave Roeder agreed to send the sponsor a draft that had been created by FDA staff. Both Pfizer and FDA staff will work of drafting a patient package insert concurrently.

Minutes Preparation: /S/
David Roeder

Concurrence Chair: /S/ 7/1/99
Robert Temple, M.D.

dr/6-22-99

RD: MGordon/6-22-99
SChen/6-22-99
RTemple/6-24-99

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

APR 21 1999

Minutes of a Meeting Between Pfizer and the FDA

Date of Meeting: April 7, 1999

Application: NDA 20-931
Tikosyn (dofetilide) Capsules

Applicant: Pfizer

Subject: Dissolution Specifications and Methods

Participants:

FDA

Patrick Marroum, Ph.D., HFD-860, Clinical Pharmacology Team Leader
Emmanuel Fadiran, Ph.D., HFD-860, Clinical Pharmacologist
Kasturi Srinivasachar, HFD-810, Chemistry Team Leader
Stuart Zimmerman, HFD-810, Chemist
David Roeder, HFD-110, Regulatory Health Project Manager

Pfizer

Dr. R.C. Weaver, Section Head, Developmental Research
Dr. J.C. Berridge, Senior Director, Analytical R & D, Developmental Research
Dr. William Murphy, Regulatory Affairs

Background

An approvable letter was issued to Pfizer for NDA 20-931 on March 5, 1999, in which we asked that they set an interim dissolution method, medium and specification of: USP Apparatus I (basket) at 100 rpm in hydrochloric acid; Q % at minutes. We also asked that they submit (after NDA approval) additional dissolution data in three media (water, acid and buffer) with and without an enzyme (pepsin in water and pH $\leq$ 6.8 or pancreatin in pH $\geq$ 6.8). The "cross-linked" capsule formulation with low dissolution (mean % dissolved at 45 minutes = 30%) and the capsules with isolated hydrophobic effect (mean % dissolved at 45 minutes = 36%) as well as stability samples that show evidence of "cross-linking" should be used to develop the optimum dissolution conditions.

The sponsor asked to meet to discuss this recommendation.

Meeting

Dr. Marroum explained the reason for asking the firm to do additional work prior to finalizing the dissolution method and specification. The method that the sponsor proposes to use is not adequately discriminatory. Bioequivalence studies have shown that capsules that do not dissolve completely under these conditions are still bioequivalent to those that are completely dissolved in the proposed medium. He stressed that, although they do not need to develop an *in vivo/in vitro* correlation, they do need to develop a method that shows a relationship to *in vivo* performance. We do not want to delay approval of the NDA, but the sponsor should do additional studies to develop a better method, and this can be done without delaying approval of the NDA.

Pfizer representatives gave an overview of the development of their dissolution methods and specifications. During development, they found that dissolution could be affected by a stability effect or a manufacturing effect. *In vitro* and *in vivo* studies showed that, although the dissolution between these different batches was quite different, they were still bioequivalent, although capsules showing a stability effect had a Tmax that was delayed from 2.5 to 3.5

hours. They were able to optimize their manufacturing process to reduce the incidence and severity of the manufacturing effect, but the stability effect was due to changes in the capsule shell properties and water uptake by the excipients. They set a dissolution method that would accept capsules showing a manufacturing effect, but reject those showing a stability effect.

Drs. Marroum and Fadiran pointed out again that the firm's proposed method is not adequately discriminatory, and Pfizer would have a difficult time supporting manufacturing changes in the future if they cannot assure us that they have the most discriminatory dissolution method that is possible. They also pointed out that with the current method and specification there is a potential to reject batches that fail the dissolution test but are actually bioequivalent to batches that pass the proposed specification.

The sponsor agreed to accept the FDA's proposed method and specification on an interim basis. They also agreed to propose (after NDA approval) an experimental design for optimizing the method and specification. The FDA representatives agreed to review this proposal and provide comments. This experimental work will be conducted and the results submitted to the FDA within one year after NDA approval, at which point a final dissolution method and specification will be determined. The approval letter will note the approved interim method and specification and acknowledge Pfizer's agreement to propose an experimental plan for determining the final method and specification.

Minutes preparation: /S/
David Roeder

Concurrence Chair: /S/
Patrick Marroum, Ph.D.

dr/4-14-99/4-20-99

RD: EFadiran/4-14-99
PMarroum/4-15-99
SZimmerman/4-16-99
KSrinivasachar/4-16-99

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

AUG 5 1999

Minutes of a Telephone Conference Call Between Pfizer and the FDA

Date of Telecon: July 14, 1999

Application: NDA 20-931
Tikosyn (dofetilide) Capsules

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

Subject: Labeling

Participants:

FDA

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation I
Shaw Chen, M.D., Ph.D., HFD-110, Medical Group Leader
Maryann Gordon, M.D., HFD-110, Medical Officer
Akinwole Williams, M.D., HFD-110, Medical Officer
Emmanuel Fadiran, Ph.D., HFD-860, Clinical Pharmacologist
David Roeder, HFD-110, Regulatory Health Project Manager

Pfizer

Dr. Cheryl Graham (RAD, Groton)
Dr. Bradley Marchant (GCTL, Sandwich)
Dr. Barbara LePetri (Medical, NY)
Ms. Rita Wittich (DRAD, NY)
Dr. Paul Nitschmann (DRAD, NY)
Dr. Inna Kissen (DRAD, NY)
Dr. William Murphy (RSR, Groton)
Ms. Marie-Caroline Sainpy (PPG, NY)
Ms. Sabrina Allan (Legal, NY)

Background

On June 15, 1999, labeling comments were sent to Pfizer via fax. On July 7, 1999, Pfizer responded with a counterproposal. Comments from the Agency regarding the July 7 submission were sent to the sponsor on July 13 and 14, 1999. The purpose of this telephone conference was to come to a resolution regarding the content of the package insert.

Meeting

The following labeling issues were discussed:

Box Warning: The final sentence of the box warning was replaced with the following text:

> Tikosyn is only available to hospitals and prescribers who have received appropriate Tikosyn dosing and treatment initiation education. See **DOSAGE AND ADMINISTRATION.**

Table 2: Pfizer asked if they would be able to include the 6-month data. They would also want to include the data on D/C for "other." Dr. Temple invited them to submit several versions, and a decision could be made at that time. Also, depending on what is included in the table, the text describing it will probably have to be revised to provide an accurate description of the table.

It was agreed that the first paragraph following the table would be revised to read as follows:

> Table 3 and Figures 3 and 4 show, by randomized dose, the effectiveness of Tikosyn in maintaining the NSR using Kaplan Meier analysis, which shows results in patients remaining on treatment.

CLINICAL STUDIES: In the description of the DIAMOND studies in the CLINICAL STUDIES section of the labeling, it was agreed that the applicant would include all cause hospitalizations in the discussion of hospitalization rates.

INDICATIONS:

> The subheading and the first sentence of the INDICATIONS section was revised to read as follows:
>
> **Maitenance of Normal Sinus Rhythm (delay in AF/AFl recurrence)**
>
> " [AF/AFl]" was added to the parenthetical statement in the first sentence of the INDICATIONS section to define atrial fibrilation/atrial flutter.
>
> Dr. Temple was concerned that the words "all recurrences" in the last sentence of the INDICATIONS section is too strong. The firm agreed to propose a revision.

PRECAUTIONS: Drug Interactions: The sponsor agreed to propose revised wording for the subsection regarding digoxin.

ADVERSE EVENTS: Dr. Temple asked the firm to include a paragraph listing adverse events occurring greater than 2%, but no more than placebo.

DOSAGE AND ADMINISTRATION: Dr. Temple asked the sponsor to include some language in the early part of this section that would mention that the usual recommended dose is 500 mcg BID modified as appropriate based on the algorithm, and that for consideration of a lower dose, see the Special Considerations subsection. The sponsor did not agree with Dr. Temple's recommended wording for the Special Considerations subsection; they agreed to make a counterproposal.

Conclusion

Pfizer agreed to the rest of Dr. Temple's comments that had been included in the faxes of July 13 and 14. They agreed to submit revised draft labeling based on this discussion.

Minutes Preparation: /S/
David Roeder

Concurrence Chair: /S/ 8/5/99
Robert Temple, M.D.

dr/7-18-99/7-28-99

RD: EFadiran/7-20-99
AWilliams/7-20-99
MGordon/7-20-99
SChen/7-20-99
RTemple/7-27-99

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

AUG 5 1999

Minutes of a Telephone Conference Call Between Pfizer and the FDA

Date of Telecon: July 19, 1999

Application: NDA 20-931
Tikosyn (dofetilide) Capsules

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

Subject: Labeling

Participants:

FDA

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation I
Shaw Chen, M.D., Ph.D., HFD-110, Medical Group Leader
Maryann Gordon, M.D., HFD-110, Medical Officer
Akinwole Williams, M.D., HFD-110, Medical Officer
David Roeder, HFD-110, Regulatory Health Project Manager

Pfizer

Dr. Cheryl Graham (RAD, Groton)
Dr. Bradley Marchant (GCTL, Sandwich)
Dr. Barbara LePetri (Medical, NY)
Ms. Rita Wittich (DRAD, NY)
Dr. Paul Nitschmann (DRAD, NY)
Dr. Inna Kissen (DRAD, NY)
Dr. William Murphy (RSR, Groton)
Ms. Sabrina Allan (Legal, NY)
Ms. Marie-Caroline Sainpy (PPG, NY)
Dr. Til Friedrich (Medical, NY)

Background

A telephone conference call was held with Pfizer on July 14, 1999 to discuss the content of the dofetilide package insert. Pfizer faxed a revised draft to the Agency on July 16, 1999. Dr. Temple's comments on this draft were faxed to the sponsor on July 18. A telephone conference call was held to discuss this draft.

Telecon

Page 12. Those revisions that were acceptable are labeled "ok" in the draft. On page 12 of the draft, Dr. Temple asked if the sponsor could include the total hospitalizations for DIAMOND MI. Pfizer agreed to collecting the data and including it, but this may take some time.

Page 13. Dr. Temple had some questions as to the adequacy of the term "highly symptomatic." After discussing possible alternatives, it was agreed that the current text was acceptable. Pfizer agreed to add "(see CLINICAL TRIALS) at the end of the INDICATIONS section.

Page 17. Pfizer agreed to accept Dr. Temple's proposal.

Page 21. Pfizer agreed to accept Dr. Temple's proposal.

Page 22. Pfizer agreed to accept Dr. Temple's proposal.

Page 23. Pfizer agreed to accept Dr. Temple's proposal.

Page 26. The following text was proposed for the Special Considerations subsection:

> The dosing algorithm shown above should be used to determine the indivualized dose of Tikosyn. In clinical trials (see CLINICAL STUDIES), the highest dose of 500 mcg BID Tikosyn, as modified by the dosing algorithm, led to greater effectiveness than lower doses of 125 or 250 mcg BID as modified by the algorithm. The risk of torsade de pointes, however, is related to dose as well as to patient characteristics (see WARNINGS). Physicians, in consultation with their patients, may therefore in some cases choose doses lower than determined by the algorithm. It is critically important that if at any time this lower dose is increased, the patient needs to be rehospitalized for three days. Previous toleration of higher doses does not eliminate the need for rehospitalization.

Dr. Temple noted that he would like to discuss this proposal with Dr. Lipicky. Pfizer representatives said that they would have to clear this wording with their management.

Pediatric Studies

The applicant must comply with the December 2, 1998 Federal Register Notice, "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients." All NDAs approved after April 1, 1999 must conduct pediatric studies unless they receive a waiver from the FDA. Submission of these studies can be deferred until after approval. Pfizer had not yet determined whether they would request a deferral or a waiver. Dr. Temple said that the FDA staff would look into the possibility of our granting a deferral that would leave open the option of our granting a waiver after approval.

Conclusion

Package Insert: Pfizer representatives will confer with their management to get concurrence on the changes discussed at this meeting. Dr. Temple will discuss them with Dr. Lipicky.

Patient Package Insert: The draft patient package insert is currently being reviewed by DDMAC. Their comments would be transmitted to Pfizer as soon as possible.

Pediatric Rule: Mr. Roeder will look into the possibility of granting a deferral that leaves open the option of granting a waiver after approval.

Addendum

Mr. Roeder confirmed that pediatric studies could be deferred until further information is obtained regarding the safety and effectiveness of the drug in adults.

Minutes preparation: /S/
David Roeder

Concurrence Chair: /S/ 8/5/99
Robert Temple, M.D.

dr/7-21-99/7-28-99/8-5-99

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

SEP 2 1999

Minutes of a Telephone Conference Call Between Pfizer and the FDA

Date of Meeting: August 11, 1999

Application: NDA 20-931
Tikosyn (dofetilide) Capsules

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

Topic: Patient Package Insert

Participants:

FDA

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation I
Maryann Gordon, M.D., HFD-110, Medical Officer
Janet Norden, HFD-40, Regulatory Review Officer
Nancy Ostrove, HFD-40, Branch Chief
Edward Fromm, HFD-110, Consumer Safety Officer
David Roeder, HFD-110, Regulatory Health Project Manager

Pfizer

Ms. Rita Wittich (DRAD, NY)
Dr. Barbara LePetri (Medical, NY)
Ms. Marie-Caroline Sainpy (PPG)
Dr. Paul Nitschmann (DRAD, NY)
Dr. Inna Kissen (DRAD, NY)
Dr. William Murphy (RSR, Groton)
Ms. Sabrina Allan (Legal, NY)

Background

Pfizer faxed a draft patient package insert (PPI) to the Agency on July 8, 1999. This draft was revised by the Agency and sent to the firm . Pfizer responded with a revised draft on July 29, 1999 which was again revised by the Agency. A telephone conference call was scheduled in an attempt to come to final agreement on the PPI.

Meeting

The FDA's version of the PPI (attached) was discussed and it was agreed that the first three sentences under **What is the most important information I should know about Tikosyn** would be revised to read:

Because you have irregular heart beats (atrial fibrillation) that are troublesome to you, Tikosyn has been prescribed to help your heart beat in a normal way. However, in some patients Tikosyn can cause a new kind of abnormal heart beat which **can be serious or can even cause death**. You may feel these as a fast beating of the heart with lightheadedness and fainting.

There was discussion about the fourth sentence of that paragraph:

—

It was agreed that Pfizer would propose a revision of that statement.

Under **Who should not take Tikosyn**, there was some disagreement about the discussion of risk and benefit. Dr. Temple said that it was important to include a discussion of that concept. He believed that the current wording was appropriate. There was also some disagreement concerning the first bullet item of that section. It was agreed that Pfizer would propose a revision of that statement.

Other changes were agreed to as indicated in the attached marked-up draft.

Minutes preparation: /S/
David Roeder

Concurrence Chair: /S/
Robert Temple, M.D.

dr/8-25-99

RD: JNorden
RTemple

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

DNOEDFR

JUN 15 1999

MEMORANDUM

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

Date: June 15, 1999
From: Shaw T. Chen, M.D., Ph.D., Medical Team Leader, HFD-110 STC
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)

This is in response to some of the questions in your memo of June 14 to Dr. Lipicky.

F. Clinical Studies

About the DIAMOND AF subpopulations, the total number of patients with AF/AFL at baseline was 506. The confusion is because not all (or majority) of these were admitted to a *pre-specified substudy*. (see Page 67-82 of Dr. Williams' review). The substudy was designed to look at the anti-arrhythmic efficacy, with mortality/morbidity as safety parameters. For some unclear reasons (unblinding because of conversion therapy?), only 178 (97 dofetilide, 81 placebo) were entered, with at least 1/3 recruited after randomization in the main study. In this small subset, there were more deaths in the dofetilide group (34/96 vs 21/81, Dr. Williams' Table 68). This was a surprise and not consistent with either the number for the overall DIAMOND-AF subgroup, nor the other DIAMOND findings. Since I could not see any perceivable distinction between this small subset (178) and all DIAMOND AF/AFL patients (506) (neither was truly prospectively randomized for the substudy), I have elected to look only at *all AF/AFL patients in DIAMOND* in my secondary review. As you know, there was no treatment difference in mortality in the latter (506 patients). About the dosage, it is correct that DIAMOND-AF patients were all treated with 250 mcg of dofetilide, not 500 mcg for those without AF/AFL.

H. Use in Females

The following data and statements are from page 21 of my secondary review, which summarize the gender difference in proarrhythmic risk:

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