CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20931

CHEMISTRY REVIEW(S)
DIVISION OF CARDIO-RENAI DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

**NDA #: 20-931**

<table>
<thead>
<tr>
<th>SUBMISSION TYPE</th>
<th>DOCUMENT DATE</th>
<th>CDER DATE</th>
<th>ASSIGNED DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORIGINAL (PRE-)</td>
<td>25-NOV-97</td>
<td>26-NOV-97</td>
<td>01-DEC-97</td>
</tr>
<tr>
<td>NC</td>
<td>04-MAR-98</td>
<td>Transfer of NDA ownership notice</td>
<td></td>
</tr>
<tr>
<td>ORIGINAL (Full)</td>
<td>09-MAR-98</td>
<td>09-MAR-98</td>
<td>11-MAR-98</td>
</tr>
<tr>
<td>AMENDMENT</td>
<td>20-MAY-98</td>
<td>21-MAY-98</td>
<td>22-MAY-98</td>
</tr>
<tr>
<td>AMENDMENT</td>
<td>03-JUN-98</td>
<td>04-JUN-98</td>
<td>06-JUN-98</td>
</tr>
<tr>
<td>AMENDMENT</td>
<td>13-OCT-98</td>
<td>14-OCT-98</td>
<td>16-OCT-98</td>
</tr>
<tr>
<td>AMENDMENT</td>
<td>27-OCT-98</td>
<td>28-OCT-98</td>
<td>29-OCT-98</td>
</tr>
<tr>
<td>AMENDMENT</td>
<td>12-NOV-98</td>
<td>13-NOV-98</td>
<td>15-NOV-98</td>
</tr>
<tr>
<td>AMENDMENT</td>
<td>23-NOV-98</td>
<td>24-NOV-98</td>
<td>25-NOV-98</td>
</tr>
<tr>
<td>AMENDMENT</td>
<td>24-NOV-98</td>
<td>25-NOV-98</td>
<td>26-NOV-98</td>
</tr>
<tr>
<td>AMENDMENT</td>
<td>07-DEC-98</td>
<td>08-DEC-98</td>
<td>09-DEC-98</td>
</tr>
</tbody>
</table>

**NAME & ADDRESS OF APPLICANT:** Pfizer Pharmaceuticals Production Corporation Limited.
Street Address: Ringaskiddy
City, State, ZIP - County Cork, Ireland

**DRUG PRODUCT NAME**
- Proprietary: Tikosyn
- Established: dofelitide
- Code Name/#: UK-68,798
- Chem Type/Ther Class: 1S

**PHARMACOL. CATEGORY/INDICATION:** Class III Antiarrhythmic Agent

**DOSAGE FORM:** Capsules
**STRENGTHS:** 0.125, 0.25 and 0.5mg
**ROUTE OF ADMINISTRATION:** Oral
**Rx/OTC:** X Rx ___ OTC
**SPECIAL PRODUCTS:** Yes ___ No

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WT.**

\[ N\left[2-(2-(4-(methanesulphonamido)phenoxy)N-methylethlamino)ethyl\right]phenyl)methanesulphonamide \]

**Structural Formula**
The structural formula of dofelitide is given below:

![Structural Formula](image)

**Molecular Formula and Molecular Weight**

<table>
<thead>
<tr>
<th>Molecular Formula of Dofetilide:</th>
<th>C_{96}H_{92}ClO_{27}N_{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Weight of Dofetilide:</td>
<td>441.8</td>
</tr>
</tbody>
</table>

**SUPPORTING DOCUMENTS:**
<table>
<thead>
<tr>
<th>Type/Number</th>
<th>Subject</th>
<th>Holder</th>
<th>Status (From cross-checks)</th>
<th>Review Date</th>
<th>Letter Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND</td>
<td>dofetilide</td>
<td>Pfizer</td>
<td>Adequate</td>
<td>Code 1</td>
<td>N/A</td>
</tr>
<tr>
<td>DMF</td>
<td>Plastic Bottles</td>
<td></td>
<td>Adequate</td>
<td>&quot;</td>
<td>N/A</td>
</tr>
<tr>
<td>DMF</td>
<td>Plastic Bottles</td>
<td></td>
<td>Adequate</td>
<td>&quot;</td>
<td>N/A</td>
</tr>
<tr>
<td>DMF</td>
<td>Plastic Bottles</td>
<td></td>
<td>Adequate</td>
<td>&quot;</td>
<td>N/A</td>
</tr>
<tr>
<td>DMF</td>
<td>Plastic Bottles</td>
<td></td>
<td>Adequate</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>DMF</td>
<td>Plastic Bottles</td>
<td></td>
<td>Adequate</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>DMF</td>
<td>Plastic Bottles</td>
<td></td>
<td>Adequate</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>DMF</td>
<td>Bottle Closure</td>
<td></td>
<td>Adequate</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>DMF</td>
<td>Bottle Closure</td>
<td></td>
<td>Adequate</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>DMF</td>
<td>Bottle Closure</td>
<td></td>
<td>Adequate</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>DMF</td>
<td>Bottle Closure</td>
<td></td>
<td>Adequate</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>DMF</td>
<td>Liner</td>
<td></td>
<td>Adequate</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>DMF</td>
<td>liner</td>
<td></td>
<td>Adequate</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>DMF</td>
<td>Liner</td>
<td></td>
<td>Adequate</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>DMF</td>
<td>Desiccant</td>
<td></td>
<td>Adequate</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>DMF</td>
<td>Aclar Blister</td>
<td></td>
<td>Adequate</td>
<td>Code #2</td>
<td>N/A</td>
</tr>
<tr>
<td>DMF</td>
<td>Foil Backing</td>
<td></td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>DMF</td>
<td>Foil Blister</td>
<td></td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>&quot;</td>
<td>Foil Backing</td>
<td></td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>DMF</td>
<td>Foil Backing</td>
<td></td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>DMF</td>
<td>Foil Backing</td>
<td></td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>DMF</td>
<td>Capsule Shell (BSE)</td>
<td></td>
<td>&quot;</td>
<td>Code# 3</td>
<td>&quot;</td>
</tr>
<tr>
<td>DMF</td>
<td>Capsule Shell (BSE)</td>
<td></td>
<td>&quot;</td>
<td>Code #4</td>
<td>&quot;</td>
</tr>
<tr>
<td>DMF # (Continued)</td>
<td>Subject (continued)</td>
<td>Holder (Continued)</td>
<td>Status (continued)</td>
<td>Rev Date Continue</td>
<td>Ltr Date continued</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------</td>
<td>--------------------</td>
<td>--------------------</td>
<td>-------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>DMF</td>
<td>Black Ink</td>
<td></td>
<td>‘‘</td>
<td>Code #3</td>
<td>‘‘</td>
</tr>
<tr>
<td>DMF</td>
<td></td>
<td>Pfizer</td>
<td>Inspection is Adequate</td>
<td>No need to review</td>
<td>N/A</td>
</tr>
<tr>
<td>DMF</td>
<td>Contract Packager</td>
<td></td>
<td>‘‘</td>
<td>Code #3</td>
<td>‘‘</td>
</tr>
<tr>
<td>DMF</td>
<td>Contract Packager</td>
<td></td>
<td>‘‘</td>
<td>Code #3</td>
<td>‘‘</td>
</tr>
<tr>
<td>DMF</td>
<td></td>
<td>Pfizer</td>
<td>N/A</td>
<td>No need to review</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Code #1** These are common DMFs that have been indicated to offer no particular potential problems since they are currently used across a wide number of approved NDAs by the applicant. It is assumed that their evaluative review status continues to be adequate without checking out each DMF.

**Code #2** This grouping of DMFs was assessed using the evaluative tools available (e.g., electronic file system with Excalibur search engines to check the regulatory review status across different NDAs for common packaging components). Then, a decisional basis for suitability was documented in the packet entitled: “Notes To File About Packaging DMFs for NDA 20-931” which was filed in the HFD-110 Div File for NDA 20-931 on 6/12/98. This approach was taken to streamline the evaluative process in anticipation of the need to rapidly reach assessment outcome results for a drug product that potentially would be given a priority rating and hence be placed on a fast track schedule. It was found that the needed supporting information was available - as determined by this stop-gap measure. In the event that a more conventional review would be needed to provide for an actual review to be filed in a DMF and hence more available to other reviewers, then it is planned to complete such a formal review in the future - perhaps when the next follow-up review is prepared for this NDA 20-931.

**Code #3** This code deals with DMFs that are not considered to be problematic since they relate to well-known and established process operations. Some will be evaluatively revisited under the next Chemistry Review #2 (e.g., DMFs).

**Code #4 - DMF** This was added after the NDA was submitted and deals with the use of the hard gelatin capsule manufacture by

In this regard, the Chemistry Review of 10/8/92 indicates the DMF is satisfactory. The representative, Mr. Chris Kotevich, was contacted on 12/16/98 and requested to update their LOA to reflect the correct Corporate name for the applicant since it is the Ringaskiddy, Ireland name. This will be done. There is no other reason to provide for an additional Chemistry Review for this DMF. Also, there is provided a FAX of 12/18/98 from Chris Kotevich that documents the firm’s compliance with the FDA/BSE regulations

**RELATED DOCUMENTS:** INDs

**CONSULTS:** None needed
REMARKS:

A number of issues were brought to the attention of the applicant as the review was ongoing. Some of these matters were documented as facsimiles. The content of these concerns are normally repeated in the applicant’s response to provide a sense of continuity.

FDA/CMC PRE-APPROVAL COMMUNICATIONS TO THE APPLICANT

<table>
<thead>
<tr>
<th>Type/Date Sent</th>
<th>Issue Definition</th>
<th>Draft Resolution Status*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAX 1/12/98</td>
<td>Pre-approval Inspection</td>
<td>Inspection undertaken</td>
</tr>
<tr>
<td>FAX 4/30/98</td>
<td>Stability Requests</td>
<td>Pending updated data</td>
</tr>
<tr>
<td>FAX 4/28/98</td>
<td>Photo-stability (MV)</td>
<td>Additional questions</td>
</tr>
<tr>
<td>FAX 5/4/98</td>
<td>Excipient Controls</td>
<td>Response is adequate</td>
</tr>
<tr>
<td>FAX 5/5/98</td>
<td>Methods Validation</td>
<td>Matter resolved</td>
</tr>
<tr>
<td>FAX 5/11/98</td>
<td>CBE protocol issues</td>
<td>Matter resolved for now</td>
</tr>
<tr>
<td>FAX 5/12/98</td>
<td>Packaging (child resistant)</td>
<td>Resolved</td>
</tr>
<tr>
<td>Mail Packet-6/11/98</td>
<td>CBE Protocol Guidance</td>
<td>Resolved / NDA approval</td>
</tr>
<tr>
<td>FAX 10/7/98</td>
<td>Innerseal Protocol data</td>
<td>Resolved</td>
</tr>
<tr>
<td>FAXA 12/10/98 (SZ)</td>
<td>Container/closure issues</td>
<td>Outstanding as of 1/6/98</td>
</tr>
</tbody>
</table>

ONGOING EVALUATIVE CONCERNS: Several CMC issues need additional attention and will be covered in the next Chemistry Review #2. These matters are outlined here. They will be voiced to the applicant for resolution. (1) 500 count designation - submission of 11/23/98, (2) Need to provide revised interim dissolution specifications, (3) Plans to use (4) Need for Expressing the expiration date in the How Supplied section of the package insert, (5) Need to include the “cold form foil” blister – not just Aclar blisters - in the How Supplied section, (6) Need to provide revised labels in final printed form.

CONCLUSIONS & RECOMMENDATIONS: This NDA is considered to be approvable from the standpoint of the chemistry and manufacturing controls issues involved pending the satisfactory inspection of the firm’s facility in Puerto Rico and the submission of additional information - above ongoing concerns and issues as expressed in the Fax of 12/10/98 from the reviewer. The validation of the applicant’s analytical methods is pending and does not impact on the NDA approval process.

cc.
Org. NDA 20-931
HFU-110/Division File
HFU-110/7Zimmerman 1/6/99
HFU-110/PM DRoeder
HFU-110/KSrinivasachar
HFU-810/CHoiberg, DNDC1 Director
R/D Init by: KSrinivasachar 1/12/99

Filename#1: (relates to the bulk drug substance): Dodrug2e(Pages 1-25) Filename#2 (relates to drug product): DOPFDT, (Pages 26-69) under My Documents
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Continued Review of Chemistry, Manufacturing, and Controls

NDA #: 20-931

DATE: 2/22/99
REVIEWER: Stuart Zimmerman

ADDENDUM TO CHEMISTRY REVIEW #2 FOR NDA 20-931:

NAME & ADDRESS OF APPLICANT:
Pfizer Pharmaceuticals Production Corporation Limited.
Street Address: Ringaskiddy
City, State, ZIP - County Cork, Ireland

DRUG PRODUCT NAME
Proprietary: Tikosyn
Established: dofetilide
Code Name/#: UK-68,798
Chem.Type/Ther.Class: 1S

PHARMACOL. CATEGORY/INDICATION: Class III Antiarrhythmic Agent
DOSAGE FORM: Capsules
STRENGTHS: 0.125, 0.25 and 0.5mg
ROUTE OF ADMINISTRATION: Oral
Rx/OTC: ___ X Rx ___ OTC
SPECIAL PRODUCTS:
Yes ___ No

CHEMICAL NAME, STRUCTURAL FORMULA

The chemical name for dofetilide is:

Structural Formule
The structural formula of dofetilide is given below:

Molecular Formule and Molecular Weight
Molecular Formule of Dofetilide: C32H35NO7S,
Molecular Weight of Dofetilide: 441.6

SUPPORTING DOCUMENTS: Same as in Chemistry Review #1
CONTINUED DISCUSSION: Several topics are covered to Help account for Outstanding Questions:

STABILITY EVALUATIVE REMARKS CONCERNING WATER CONTENT LEVELS: It is considered to be necessary to deal with the moisture content issue again to help clarify the potential problem to have drug product failures based on values that may occur on extended stability testing. The applicant's specification limit is 1% %. Concerning the water content data resulting from studies conducted at 30°C/60%RH after 12 months, it is noted that there are no failures in any of the packaging configurations and there is a comfortable margin of at least % for the batches studied before failure at %. The firm's 18 month data shows no failures for the 30°C/60%RH condition as given in the 12/7/98 submission. Here, the worst case value was % at the 9 month interval for the stability lot provided on page 147. In this case, the values at 12 and 18 months had decreased to values of Such a similar peaking effect at 9 months is also seen in other related data. Hence, no firm trending effect can be established that may predict a certain failure rate based on a known trending experience. So, there is no known control problem for moisture content at this time.

STORAGE STATEMENT CONSIDERATIONS: There are several concerns relating to the applicant's wish to change their storage statement in their amendment dated 2/3/99 to "Store at controlled room temperature, 15° to 30°C (59 - 86°F)" from "Store at excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] - as previously changed by FDA suggestion. Since the firm wants to use the 30°C station, there are a number of protocol issues that need to be changed: (1) Concerning the stability protocols currently in place for conducting trials for the commercial batches, there is need for revision to include the 30°C/60%RH test condition, (2) Currently conducted trials that do not include this station out to the expiration date also need to be revised such as the trials conducted to provide for the Puerto Rico site whereby there is provision to only conduct testing for 12 months at this station, (3) The stability protocols dealing with placing batches into the routine stability program as specified in the various interchangeability protocols - and related configuration changes relating to packaging - need to be changed to include the 30°C/60%RH station extending throughout the expiry period. Another option to take to resolve this issue is for the firm to go back to the use of the storage statement that they had once used which is the one that FDA recommended - see above. This would then mean that the package insert would need to be again revised as well as all the labeling involved. The firm has been advised of these various considerations and FDA awaits their response.

DISSOLUTION SPECIFICATION ISSUE: It is noted that the FDA action letter will now contain a statement indicating that the it is expected that an interim dissolution specification will be adopted that tightens the dissolution limit to % in minutes - rather than at minutes as initially proposed. As noted in the Chemistry Review #2, the stability data provided supports this restriction. Also, in accord with the suggestions given by Dr. Fadran in his Biopharmaceutical review, there is the post-approval issue for the firm to try to revise their in-vitro dissolution method so it is better able to relate to in-vivo results. (e.g., use of different media). Any such potential revision will need to be assessed in terms of its ability to monitor continuing stability trials for the firm's ongoing trials.

SITE INSPECTION ISSUE FOR PUERTO RICO: The site has been reported to have had an inspection recently and no 483 was issued. There is still no message from OC about the approval status of this site.

FDA VALIDATION IS PENDING: The validation of the applicant's analytical methods is pending and does not impact on the NDA approval process.
CC: Org. NDA 20-931
HFD-110/Division File
HFD-110/SZimmerman
HFD-110/PM DRoeder
HFD-110/KSrinivasachar
HFD-810/CHoiberg, DNDC1 Director
HFD-810/JSimmons DNDC1 Dup Director
R/D Init by: KSrinivasachar

Filename: Addendum
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-931
REVIEW # 2

<table>
<thead>
<tr>
<th>SUBMISSION TYPE</th>
<th>DOCUMENT DATE</th>
<th>CDER DATE</th>
<th>ASSIGNED DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amendment *</td>
<td>14-DEC-98</td>
<td>15-DEC-98</td>
<td>16-DEC-98</td>
</tr>
<tr>
<td>Amendment</td>
<td>11-JAN-99</td>
<td>12-JAN-99</td>
<td>13-JAN-99</td>
</tr>
<tr>
<td>Amendment</td>
<td>27-JAN-99</td>
<td>28-JAN-99</td>
<td>30-JAN-99</td>
</tr>
<tr>
<td>Amendment</td>
<td>03-FEB-99</td>
<td>04-FEB-99</td>
<td>05-FEB-99</td>
</tr>
<tr>
<td>Amendment</td>
<td>09-FEB-99</td>
<td>Open</td>
<td>Open</td>
</tr>
</tbody>
</table>

* Submission date was not included in the Chemistry Review #1 dated 1/6/99

NAME & ADDRESS OF APPLICANT:
Pfizer Pharmaceuticals Production Corporation Limited.
Street Address: Ringaskiddy
City, State, ZIP - County Cork, Ireland

DRUG PRODUCT NAME
Proprietary: Tikosyn
Established: dofetilide
Code Name/#: UK-68,798
Chem. Type/Ther. Class: 1S

PHARMACOL. CATEGORY/INDICATION: Class III Antiarrhythmic Agent
DOSAGE FORM: Capsules
STRENGTHS: 0.125, 0.25 and 0.5mg
ROUTE OF ADMINISTRATION: Oral
Rx/OTC: ___X Rx ___ OTC
SPECIAL PRODUCTS:
Yes ___X No

CHEMICAL NAME, STRUCTURAL FORMULA

The chemical name for dofetilide is:
N-[2-[4-[[N-methyl(-2,4-dimethyl-6-phenoxypyropylden)]amino]-ethy]amino]-ethy]methylsulfonium methansulfonate

Structural Formula
The structural formula of dofetilide is given below:

```
\[\text{Molecular Formula and Molecular Weight}
Molecular Formula of Dofetilide: C_{26}H_{36}NO_{8}S
Molecular Weight of Dofetilide: 441.5\]
```

SUPPORTING DOCUMENTS: Same as in Chemistry Review #1
REMARKS:
A number of the evaluative concerns provided in this review also deal with amendments that have been cited in Chemistry Review #1 in order to provide a better profile of assessment considerations. For the sake of organizations the various submissions are listed below with a brief characterization.

- 12/14/99: Labeling Issues
- 1/11/99: This most basically deals with various FDA queries concerned with the previously submitted amendment dated 11/23/98 relating to the Puerto Rico site (e.g., container-closure system and labeling matters).
- 1/27/99: Notification that all NDA rights have been transferred to Pfizer Pharmaceuticals Production Corporation Limited, Ringaskiddy, County Cork, Ireland. and an updated (1/8/99) claim for a categorical exclusion concerning the environmental assessment.
- 2/3/99: Labeling issues and related packaging concerns:

A number of issues were brought to the attention of the applicant as the review was ongoing. Some of these matters were documented as facsimiles. These concerns are normally repeated in the applicant’s response to provide for a sense of continuity.

FDA/CMC PRE-APPROVAL COMMUNICATIONS TO THE APPLICANT

<table>
<thead>
<tr>
<th>Type/Date Sent</th>
<th>Issue Definition</th>
<th>Draft Resolution Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facsimile (12/10/99)</td>
<td>See Remarks in CR#1</td>
<td>Issues resolved</td>
</tr>
<tr>
<td>Telephone message (1-29-99)</td>
<td>Chemical name issue</td>
<td>Issue resolved</td>
</tr>
<tr>
<td>Amendment (2/3/99)</td>
<td>Response to Questions</td>
<td>Issues resolved</td>
</tr>
<tr>
<td>Facsimile (2/4/99)</td>
<td>Chemical name issue</td>
<td>Issue resolved</td>
</tr>
</tbody>
</table>

ONGOING EVALUATIVE CONCERNS: The results of the inspection of the Pfizer site in Puerto Rico need to be provided. An EES check was made on 2/5/99 and it is indicated that the site has been assigned for inspection which is currently ongoing - but this matter is still pending.

CONCLUSIONS & RECOMMENDATIONS: This NDA is considered to be approvable from the standpoint of the chemistry and manufacturing controls issues involved pending the satisfactory inspection of the firm’s facility in Puerto Rico. The validation of the applicant’s analytical methods is pending and does not impact on the NDA approval process.

/S/
Stuart Zimmerman, Ph.D.

CC: Org. NDA 20-931
HFD-110/Division File
HFD-110/SZimmerman
HFD-110/PM DRoeder
HFD-110/KSrinivasachar
HFD-810/CHOiberg, DNDC1 Director
R/D Init by: KSrinivasachar

/S/ 2-10-99

Filename: DoFETCR2 (REV 2/9/99)
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-931
REVIEW # 3

DATE REVIEWED: 3/5/99
REVIEWER: Stuart Zimmerman

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE
Amendment 04-MAR-99 05-MAR-99 05-MAR-99

NAME & ADDRESS OF APPLICANT:
Pfizer Pharmaceuticals Production Corporation Limited. (PPPI)
Street Address: Ringaskiddy
City, State, ZIP - County Cork, Ireland

DRUG PRODUCT NAME
Proprietary: Tikosyn
Established: dofetilide
Code Name/#: UK-68,798
Chem.Type/Ther.Class: 1S

PHARMACOL. CATEGORY/INDICATION: Class III Antiarrhythmic Agent

DOSE FORM:
Capsules

STRENGTHS:
0.125, 0.25 and 0.5 mg

ROUTE OF ADMINISTRATION:
Oral

Rx/OTC:
X Rx _ OTC

SPECIAL PRODUCTS:
Yes _ No

CHEMICAL NAME, STRUCTURAL FORMULA

The chemical name for dofetilide is:
methanesulfonamide.

Structural Formula
The structural formula of dofetilide is given below.

Molecular Formula and Molecular Weight
Molecular Formula of Dofetilide: C29H33N3O6
Molecular Weight of Dofetilide: 441.5

SUPPORTING DOCUMENTS: Same as in Chemistry Review #1
REMARKS: This review covers the outstanding issues remaining from Chemistry Review #2. A number of conversations were held between the reviewer and Dr. Murphy and Mr. Dennis Casey to help resolve the storage statement in the labeling for the drug product. These matters were resolved as noted by the applicant's response dated March 4, 1999. This involved several changes in the stability section (e.g., protocol changes for post-approval commercial batches and all ongoing qualification batches in order to provide for data at or beyond the proposed expiry date of 24 months.

The CMC issue of tightening the dissolution specification in terms of shortening the sampling time to minutes from minutes is based on considerations derived from a finalized and documented report from the Division of Clinical Pharmacology concerning the applicant's recent response included in the amendment dated 3/4/99.

The inspection issue for the firm's site in Puerto Rico currently resolved as noted in the report provided

CONCLUSIONS & RECOMMENDATIONS: This NDA is considered to be approvable from the standpoint of the chemistry and manufacturing controls issues involved. The firm's methods validations at FDA laboratories is still pending completion but this issue does not impact on the approvable action.

Stuart Zimmerman, Ph.D.

CC: Org. NDA 20-931
HFD-110/Division File
HFD-110/Zimmerman
HFD-110/PM DRoeder
HFD-110/KSrinivasachar
HFD-810/CHoiberg, DNDC1 Director
R/D Init by: KSrinivasachar

3-5-99
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-931
REVIEW #: 3

DATE REVIEWED: 9/14/99
REVIEWER: Stuart Zimmerman

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE

NAME & ADDRESS OF APPLICANT:
Pfizer Pharmaceuticals Production Corporation Limited.
Street Address: Ringaskiddy
City, State, ZIP - County Cork, Ireland

DRUG PRODUCT NAME
Proprietary: Tikosyn
Established: dofetilide
Code Name/#: UK-68,798
Chem. Type/Ther. Class: 1S

PHARMACOL. CATEGORY/INDICATION:
Class III Antiarrhythmic Agent

DOSAGE FORM:
Capsules

STRENGTHS:
0.125, 0.25 and 0.5mg

ROUTE OF ADMINISTRATION:
Oral

Rx/OTC:
X Rx ___ OTC

SPECIAL PRODUCTS:
Yes X No

CHEMICAL NAME, STRUCTURAL FORMULA


Structural Formula

The structural formula of dofetilide is given below:

\[
\text{Structure Image}
\]

Molecular Formula and Molecular Weight
Molecular Formula of Dofetilide: \( \text{C}_{46}\text{H}_{34}\text{N}_{12}\text{O}_{12}\)
Molecular Weight of Dofetilide: 641.8

SUPPORTING DOCUMENTS: Same as in Chemistry Review #1
REMARKS:
This review is to critically account for the draft labeling provided in reference to the FDA requests.

ONGOING EVALUATIVE CONCERNS: The Method's Validation is currently underway since samples have been reported to have been provided to the Philadelphia Laboratory; also samples need to be sent to the FDA at PR – yet no word from this lab.

CONCLUSIONS & RECOMMENDATIONS: This NDA is now considered to be acceptable from the standpoint of the chemistry and manufacturing controls issues involved. The validation of the methods is ongoing and will not withhold approval at his time.

/S/
Stuart Zimmerman, Ph.D.

CC: Org. NDA 20-931
    HFD-110/Division File
    HFD-110/SZimmerman
    HFD-110/PM DRoeder
    HFD-110/KSrinivasachar
    HFD-810/JSimmons DNDC1 Director
    R/D Init by: KSrinivasachar

Filename: NDA20931-CR#3