# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-656**

## CHEMISTRY REVIEW(S)

11/5/04

CHEMISTRY REVIEW

# NDA 21-656

## Tricor® (fenofibrate) Tablets

## Abbott Laboratories

**William M. Adams**
**Division of Metabolism and Endocrine Drug Products**
**HFD-510**

# Table of Contents

# Chemistry Review Data Sheet

1. NDA 21-656

2. REVIEW #2

3. REVIEW DATE: 04-Nov-2004

4. REVIEWER: William M. Adams

5. PREVIOUS DOCUMENTS:

| Submission(s) Reviewed | Document Date |
|---|---|
| Original Submission | 29-Oct-2003 |
| C Amendment | 16-Jan-2004 |
| BZ Amendment | 19-Apr-2004 |
| BC Amendment | 20-Apr-2004 |
| BZ Amendment | 01-Jun-2004 |
| BC Amendment | 09-Jul-2004 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| AZ Amendment | 09-Sep-2004 |
| AC Amendment | 04-Nov-2004 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Abbott Laboratories |
| Address: | Pharmaceutical Products Division<br>D214/Building AP30-1E<br>200 Abbott Park Road<br>Abbott Park, IL 60064-6157 |
| Representative: | Ernesto J. Rivera<br>Regulatory Affairs Manager |
| Telephone: | (847) 937-7847 |

8. DRUG PRODUCT NAME/CODE/TYPE:
   (a) Proprietary Name: Tricor®
   (b) Non-Proprietary Name (USAN): Fenofibrate Tablets
   (c) Code Name/# (ONDC only): N1304 (Elan) Tablets
   (d) Chem. Type/Submission Priority (ONDC only):
   Chemical Type: 3
   Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOLOGICAL CATEGORY: Lipid Altering Drug

11. DOSAGE FORM: IR, film-coated tablet

12. STRENGTH/POTENCY: 48mg and 145mg

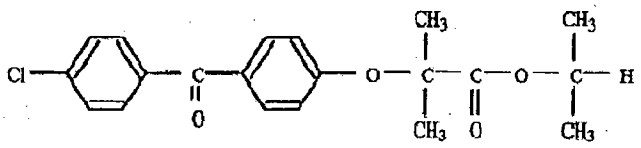
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__XX__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
2-[4-(4-chlorobenzoyl)-phenoxy]-2-methyl-propanoic acid, 1methylethyl ester
Molecular Formula: $C_{20}H_{21}ClO_4$
Molecular Weight: 360.83



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | Type | HOLDER | ITEM REFERENCE | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| | II | | | 1 | Adequate | CMC #3 dated 10/20/04 | |
| | II | | | 1 | Adequate | CMC #3 dated 10/20/04 | |
| | II | | | 1 | Adequate | CMC#2 dated 03/03/04 | --- |
| | II | | | 1 | Adequate | CMC #2 dated 10/20/04 | |
| | IV | | | 3 | Adequate | --- | --- |
| | IV | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

| NDA# | Trade Name | Established Name | Approval Date | NDA Holder |
|---|---|---|---|---|
| 19-304 (non-US sales) | Lipidil™ | 100mg HG capsule | 12/31/93 | Abbott |
| 19-304 (discontinued) | TriCor® (micronized)<br>TriCor® (micronized)<br>TriCor® (micronized) | 067mg HG capsule<br>134mg HG capsules<br>200mg HG capsule | 02/09/98<br>06/30/99<br>06/30/99 | Abbott |
| 21-203 | TriCor®<br>TriCor® | 054mg f/c tablet<br>160mg f/c tablet | 09/04/01<br>09/04/01 | Abbott |

18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | N/A | | |
| EES | Acceptable | 29-Jun-2004<br>06-Aug-2004 | OC |
| Pharm/Tox | Acceptable | 27-May-2004 | I.Antonipillai |
| Biopharm | Acceptable with comments | 02-Aug-2004 | W.Qiu |
| LNC (trade name) | Adequate | 16-Aug-2004 | D.Lewis |

| | | | |
|---|---|---|---|
| Methods Validation | Submitted to NDA | | M. Adams |
| OPDRA | Pending re 08/05/04 AMD | | |
| EA | Categorical Exclusion Granted | | |
| Microbiology | N/A | | |

19. ORDER OF REVIEW (OGD Only): N/A

# The Chemistry Review for NDA 21-656

## *The Executive Summary*

## I. RECOMMENDATIONS

### A. RECOMMENDATION & CONCLUSION ON APPROVABILITY

The proposed application should be APPROVED.

### B. RECOMMENDATION ON PHASE 4 (Post-Marketing) COMMITMENTS, AGREEMENTS &/or RISK MANAGEMENT STEPS, if Approvable

No phase 4 commitments have been proposed in the application.

The firm has agreed to perform a post approval study to assess the impact of moisture level on product performance with an endpoint of product failure. The study is to be started in the first quarter 2005 and completed by the third quarter 2005. They anticipate using the conclusion to refine the drug product specification.

## II. SUMMARY OF CHEMISTRY ASSESSMENTS

### A. DESCRIPTION OF THE DRUG PRODUCT(S) & DRUG SUBSTANCE(S)

DRUG PRODUCT

The proposed drug product is TriCor® (fenofibrate) 48mg and 145mg immediate release, film-coated tablets in a 90-count — bottle market package and 3x7-count physician sample blister package. The proposed indication is lipid alteration. The applicant states that the proposed manufacturing process was developed for them by ——— to obtain a drug product that has bioavailability comparable to the currently marketed Tricor® tablets (NDA 21-203) and will eliminate the food effects of that product.

Bulk, micronized fenofibrate is manufactured into the coated tablets in a ——process by Fournier Laboratories Ireland, Ltd [FLI] (County Cork, Ireland), then shipped to Abbott Laboratories (North Chicago, IL) for packaging into the bottle and blister package configurations. ——— will provide contract microbiological testing services. Product release and stability testing may be performed at FLI or Abbott Laboratories (Abbott park, IL) All — sites are in compliance with cGMPs. The — drug product manufacturing steps are described in FLI's type II DMF —— and summarized in the application. The —— steps of tablet manufacture are described in the application. The applicant has requested a categorical exclusion under 21 CFR 25.31(a) and certified that the FLI site meets the environmental standard of Ireland.

The —— tablet manufacturing steps are described in DMF —. ———

Packaging DMFs were not reviewed as adequate CMC information was provided in the application. Packaging is to be performed within 6 months of film-coating. Start of the drug product shelflife is the date of first manipulation of the active ingredient. Neither rework nor re-processing is proposed in the tablet manufacturing steps. The application addresses drug substance, ingredient and drug product specifications; the letters of authorization; drug product manufacturing process description and controls; method validation studies; batch analysis data; example batch records; impurity and reference standard characterizations; bulk tablet and market product packaging information; NDA and post approval stability protocols and data; and draft labels and labeling.

DRUG SUBSTANCE

Fenofibrate is 2-[4(4-chlorobenzoyl)-phenoxy]-2-methylpropanoic acid, 1-methylethyl ester. It is a white crystalline powder which is water insoluble. Bulk, un-micronized fenofibrate is manufactured by under type II DMF , under type II DMF All CMC information regarding the manufacturing and control of un-micronized and micronized drug substance is contained in the cited DMFs. Both DMFs have been reviewed and found adequate to support this application. manufacturing sites are in compliance with cGMPs. suppliers release bulk un-micronized drug substance under the current European Pharmacopoeia monograph, which adequately addresses identity, purity and potency, and have added particle size limits. There is no USP monograph for Fenofibrate. Micronized drug substance is released under particle size limits determined by the requirements of the drug product manufacturing process. The application includes details of the drug substance release specifications, batch analysis data, and qualification data for the drug substance and impurity reference standards.

### B. DESCRIPTION OF HOW THE DRUG PRODUCT IS INTENDED TO BE USED

Dosing is one tablet per day for an extended period with the maximum daily dose being the higher strength tablet. The proposed expiration date is 18 months when stored at USP controlled room temperature.

### C. BASIS FOR APPROVABILITY OR NOT APPROVAL RECOMMENDATION

With regard to CMC information, the application can be APPROVED (AP) in that complete information has been provided and all issues have been addressed.

## III. ADMINISTRATIVE

### A. REVIEWER'S SIGNATURE

William M. Adams, CMC Reviewer for HFD-510

### B. ENDORSEMENT BLOCK

M.Adams/CMC Reviewer for HFD-510
S.Moore concurrence
File: N21656_R02.doc

**C. CC BLOCK**

E.Duffy/Div Dir for DNDC2
B.Fraser/Dep Div Dir for DNDC2
V.Jimenez/PM

# 12 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Chemistry-_____*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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Mike Adams
11/5/04 12:09:13 PM
CHEMIST

Stephen Moore
11/5/04 03:57:17 PM
CHEMIST

6/12/04

CHEMISTRY REVIEW

# NDA 21-656

## Tricor® (fenofibrate) Tablets

## Abbott Laboratories

William M. Adams
Division of Metabolism and Endocrine Drug Products
HFD-510

# Table of Contents

# Chemistry Review Data Sheet

1. NDA 21-656

2. REVIEW #1

3. REVIEW DATE: 12-Aug-2004

4. REVIEWER: William M. Adams

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Original Submission | 29-Oct-2003 |
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| BZ Amendment | 19-Apr-2004 |
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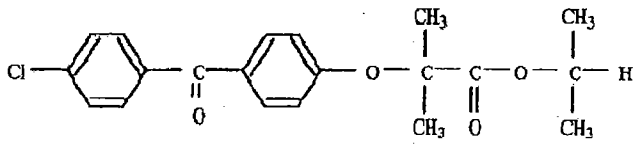

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| | II | | | 1 | Adequate | CMC #3 pending | |
| | II | | | 1 | Adequate | CMC #3 pending | |
| | II | | | 1 | Adequate | CMC#2 dated 03/03/04 | --- |
| | II | | | 1 | Deficient | CMC #1 dated 06/17/04 | DEF letter pending |
| | IV | | | 3 | Adequate | --- | --- |
| | IV | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
| | III | | | 4 | N/A | | |
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| | III | | | 4 | N/A | | |

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| LNC | N/A | | |
| Methods Validation | Submitted to NDA | | M. Adams |

| | | | |
|---|---|---|---|
| OPDRA | Pending re 08/05/04 AMD | | |
| EA | Not Submitted | | |
| Microbiology | N/A | | |

19. ORDER OF REVIEW (OGD Only): N/A

# The Chemistry Review for NDA 21-656

## *The Executive Summary*

## I. RECOMMENDATIONS

### A. RECOMMENDATION & CONCLUSION ON APPROVABILITY

The proposed application is APPROVABLE pending submission of additional CMC information listed in section III of this review.

### B. RECOMMENDATION ON PHASE 4 (Post-Marketing) COMMITMENTS, AGREEMENTS &/or RISK MANAGEMENT STEPS, if Approvable

No phase 4 commitments have been proposed in the application.

## II. SUMMARY OF CHEMISTRY ASSESSMENTS

### A. DESCRIPTION OF THE DRUG PRODUCT(S) & DRUG SUBSTANCE(S)

DRUG PRODUCT

The proposed drug product is TriCor® (fenofibrate) 48mg and 145mg immediate release, film-coated tablets in a 90-count — bottle market package and 3x7-count physician sample blister package. The proposed indication is lipid alteration. The applicant states that the proposed manufacturing process was developed for them by — to obtain a drug product that has bioavailability comparable to the currently marketed Tricor® tablets (NDA 21-203) and will eliminate the food effects of that product.

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— — — Packaging DMFs were not reviewed as adequate CMC information was provided in the application. Packaging is to be performed within 6 months of film-coating. Start of the drug product is proposed as the date of packaging. Neither rework nor re-processing is proposed in the tablet manufacturing steps. The application addresses drug substance, ingredient and drug product specifications; the letters of authorization; drug product manufacturing process description and controls; method

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### B. DESCRIPTION OF HOW THE DRUG PRODUCT IS INTENDED TO BE USED

Dosing is one tablet per day for an extended period with the maximum daily dose being the higher strength tablet. The proposed expiration date is 18 months when stored at USP controlled room temperature.

### C. BASIS FOR APPROVABILITY OR NOT APPROVAL RECOMMENDATION

The application is APPROVABLE (AE) in that the deficiencies listed in section III of this review should be addressed prior to approval. Significant deficiencies were also found in DMF [redacted] as well as the application; the drug product manufacturing process controls; the stability information; and the method validation studies.

## III. ADMINISTRATIVE

### A. REVIEWER'S SIGNATURE

_____

William M. Adams, CMC Reviewer for HFD-510

### B. ENDORSEMENT BLOCK

M.Adams/CMC Reviewer for HFD-510/12-Aug-2004
S.Moore concurrence/12-Aug-2004
V.Jimenez/PM
File: N21656_R01.doc

### C. CC BLOCK

E.Duffy/Div Dir for DNDC2
B.Fraser/Dep Div Dir for DNDC2

# 102 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Chemistry-* REV 1

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/

Mike Adams
8/12/04 02:47:23 PM
CHEMIST

Stephen Moore
8/12/04 05:53:56 PM
CHEMIST