

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-151

CSO LABELING REVIEW(S)

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **76-151**

Date of Submission: **July 30, 2001**

Applicant's Name: **TorPharm**

Established Name: **Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-Day Dosage) 120 mg, 180 mg, 240 mg, and 300 mg**

Labeling Deficiencies:

1. GENERAL COMMENTS

- a. Your proposed proprietary name "Dilt CD" has been submitted to the Office of Post-Marketing Drug Risk Assessment (OPDRA) for their review and comment. We will notify you of their recommendations when available. We will not ask for labels and labeling in final print pending the findings of OPDRA.
- b. The phrase "(Once-a-day dosage)" should not be part of the established name but it should be used in conjunction with it - e.g., "Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage)".

2. CONTAINER 30s and 500s

- a. See GENERAL COMMENTS 1 (a) above.
- b. Place the statement "(Once-a-day-dosage)" immediately beneath the established name and separate from it. See GENERAL COMMENTS 1 (b) above.
- c. The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use packaging). Your proposed containers of 30 appear to be in this category. Therefore, we believe that this package must comply with the Act. You have not indicated in your submission whether or not these containers have child-resistant closures. Please comment.

3. INSERT

a. GENERAL COMMENT

See GENERAL COMMENTS above.

b. DESCRIPTION

- i. There is no need to list the alcohols in the listing of inactive ingredients.
- ii. Does "n-butyl" represent "n-butyl alcohol"? If so please see comment 3(b)(i) above.

iii. You are required to state the USP Drug Release Test number with which your product complies in this section or include the following statement as the last sentence in this section: "USP Drug Release test pending."

c. ADVERSE REACTIONS

Third paragraph - "i.e.," rather than ' —

d. OVERDOSAGE

i. Bradycardia - "(0.6 to 1 mg)" (delete trailing zeros)

ii. Hypotension

A). "e.g." rather than ' —

B). "norepinephrine" rather than ' _____

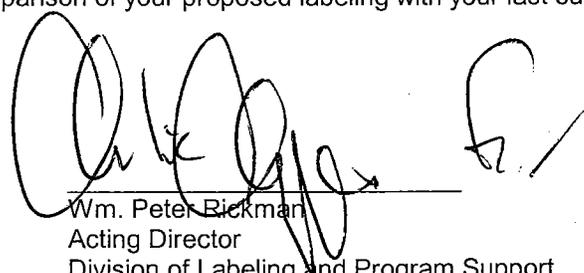
e. DOSAGE AND ADMINISTRATION

Concomitant Use With Other Cardiovascular Agents, Sublingual NTG - "... (Diltiazem Hydrochloride Extended-Release Capsules USP)(Once-a-day-dosage) therapy.

Please revise your container labels and insert labeling, as instructed above, and submit 4 draft copies of each labeling piece.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **76-151**

Date of Submission:

August 29, 2001 G.V. 10/5
~~July 30, 2001~~

Applicant's Name: **TorPharm**

Established Name: **Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-Day Dosage) 120 mg, 180 mg, 240 mg, and 300 mg**

Labeling Deficiencies:

1. GENERAL COMMENTS

- a. Your proposed proprietary name "Dilt CD" has been submitted to the Office of Post-Marketing Drug Risk Assessment (OPDRA) for their review and comment. We will notify you of their recommendations when available. We will not ask for labels and labeling in final print pending the findings of OPDRA.
- b. The phrase "(Once-a-day dosage)" should not be part of the established name but it should be used in conjunction with it - e.g., "Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage)".

2. CONTAINER 30s and 500s

- a. See GENERAL COMMENTS 1 (a) above.
- b. Place the statement "(Once-a-day-dosage)" immediately beneath the established name and separate from it. See GENERAL COMMENTS 1 (b) above.
- c. The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use packaging). Your proposed containers of 30 appear to be in this category. Therefore, we believe that this package must comply with the Act. You have not indicated in your submission whether or not these containers have child-resistant closures. Please comment.

3. INSERT

a. GENERAL COMMENT

See GENERAL COMMENTS above.

b. DESCRIPTION

- i. There is no need to list the alcohols in the listing of inactive ingredients.
- ii. Does "n-butyl" represent "n-butyl alcohol"? If so please see comment 3(b)(i) above.

iii. You are required to state the USP Drug Release Test number with which your product complies in this section or include the following statement as the last sentence in this section: "USP Drug Release test pending."

c. ADVERSE REACTIONS

Third paragraph - "i.e.," rather than _____

d. OVERDOSAGE

i. Bradycardia - "(0.6 to 1 mg)" (delete trailing zeros)

ii. Hypotension

A). "e.g." rather than ' _____

B). "norepinephrine" rather than ' _____

e. DOSAGE AND ADMINISTRATION

Concomitant Use With Other Cardiovascular Agents, Sublingual NTG - "... (Diltiazem Hydrochloride Extended-Release Capsules USP)(Once-a-day-dosage) therapy.

Please revise your container labels and insert labeling, as instructed above, and submit 4 draft copies of each labeling piece.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY

Was this approval based upon a petition? No
 What is the RLD on the 356(h) form: Cardizem® CD
 NDA Number: 20-062
 NDA Drug Name: Cardizem® CD (Diltiazem Hydrochloride Extended-release Capsules USP)
 NDA Firm: Hoechst Marion Roussel
 Date of Approval of NDA Insert and supplement #: 8/24/99 (S-027)
 Has this been verified by the MIS system for the NDA? Yes
 Was this approval based upon an OGD labeling guidance? No
 Basis of Approval for the Container Labels: side-by-sides and container labels in file folder
 Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?	X		
Has the name been forwarded to the Labeling and Nomenclature Committee? YES If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns? NEED CRC FOR 30s CONTAINER SIZE	X		
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X	X	

11. Generic firms have been asked to place the text (once-a-day dosage) in conjunction with the established name.

Date of Review: 9-14-01

Date of Submission: 7-30-01

Primary Reviewer: Adolph Vezza

Date:

A. Vezza

9/17/01

Team Leader: Charlie Hoppes

Date:

Charlie Hoppes

9/17/01

cc: ANDA: 76-151
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)
aev/9/14/01|V:\FIRMSNZ\TORPHARM\LTRS&REV\76151na1.l
Review

APPEARS THIS WAY
ON ORIGINAL

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: December 11, 2001
ANDA NUMBER: 76-151
NAME OF DRUG: Dilt CD
(Diltiazem Hydrochloride Extended-Release Capsules, USP)
120 mg, 180 mg, 240 mg, 300 mg
ANDA HOLDER: TorPharm

*****NOTE:** This review contains proprietary and confidential information that should not be released to the public.***

I. INTRODUCTION:

This consult was written in response to a request from the Office of Generic Drugs, Labeling Review Branch (HFD-613) for assessment of the tradename "Dilt CD", regarding potential name confusion with other proprietary/generic drug names.

The sponsor is proposing the name Dilt CD for diltiazem hydrochloride extended-release capsules, USP. Dilt CD is the generic drug product for the reference listed drug, Cardizem CD (as per email communication with Office of Generic Drugs, 12/10/01). Dilt CD is indicated for the treatment of hypertension and for the management of chronic stable angina. For the treatment of hypertension, dosages must be adjusted to each patient's needs, starting with 180 mg or 240 mg once daily. Dosages for the treatment of angina should also be adjusted to each patient's needs, starting with a dose of 120 mg or 180 mg once daily, and may be titrated to doses of up to 480 mg once daily. Dilt CD will be available by prescription as 120 mg, 180 mg, 240 mg, and 300 mg capsules in bottles of 30 and 500 count.

Also proposed by the sponsor was the proprietary name, _____, which OPDRA reviewed on May 23, 2001 for the 120 mg, 180 mg, and 240 mg diltiazem hydrochloride extended-release capsules, USP. (OPDRA Consult 01-0082). OPDRA had no objections to the proprietary name _____, which is equivalent to the existing drug product Diltia XT. Both _____ and Diltia XT are the generic drug products for the same reference listed drug, Dilacor XR.

II. SAFETY EVALUATOR RISK ASSESSMENT:

OPDRA has no objections to the use of the proposed proprietary name, Dilt CD. The use of "Dilt" was previously found acceptable under the proposed name "_____" (OPDRA Consult 01-0082).

"CD" is a common modifier used to express an extended-release formulation. There are many approved extended-release drug products with proprietary names that contain the modifier "CD" such as Cardizem CD, Ceclor CD, Lamictal CD, and Metadate CD. Therefore, OPDRA has no

objections to the use of the modifier "CD" for the extended-release tablet formulation. This is contingent on the fact that this drug product is truly an extended-release formulation of the reference listed drug Cardizem CD.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container label and the package insert of Dilt CD, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified an area of possible improvement, in the interest of minimizing potential user error.

1. Drugs packaged in "unit of use" bottles and dispensed on an outpatient basis, such as the 30 capsule bottles, should include Child Resistant Closures (CRC).

IV. RECOMMENDATIONS

OPDRA has no objections to the use of the proprietary name, Dilt CD, if the Division agrees that this is truly an extended-release formulation of the reference listed drug Cardizem CD.

OPDRA recommends the above packaging revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

OPDRA would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, Project Manager, at 301-827-3242.

Nora Roselle 12/11/01

Nora Roselle, Pharm.D.

Safety Evaluator

Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips 12/12/01

Jerry Phillips, R.Ph.

Associate Director for Medication Error Prevention

Office of Postmarketing Drug Risk Assessment (OPDRA)

cc: ANDA 76-151
HFD-615; Division Files/Harvey Greenberg, Project Manager

Electronic only cc:
HFD-610; Peter Rickman, Acting Division Director
HFD-613; Adolph Vezza, Labeling Review Branch
HFD-400; Nora Roselle, Safety Evaluator, OPDRA

L:\OPDRA01\ROSELLE\01-0204DILTCD\FIN.DOC

**APPEARS THIS WAY
ON ORIGINAL**

**TENTATIVE APPROVAL SUMMARY
 REVIEW OF PROFESSIONAL LABELING
 DIVISION OF LABELING AND PROGRAM SUPPORT
 LABELING REVIEW BRANCH**

ANDA Number: **76-151** Date of Submission: **February 26, 2002**

Applicant's Name: **TorPharm**

Proprietary Name: **Dilt CD**

Established Name: **Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-Day Dosage) 120 mg, 180 mg, 240 mg, and 300 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? **NO - TENTATIVE APPROVAL**

Container Labels: **30s and 500s**

Satisfactory in draft as of the February 26, 2002 submission.

Professional Package Insert Labeling:

Satisfactory in draft as of the February 26, 2002 submission.

Revisions needed post-approval: container - ensure that the strength is legible on the main panel --- PI - ensure that the print quality is adequate

BASIS OF APPROVAL

Was this approval based upon a petition? **No**

What is the RLD on the 356(h) form: **Cardizem[®] CD**

NDA Number: **20-062**

NDA Drug Name: **Cardizem[®] CD (Diltiazem Hydrochloride Extended-release Capsules USP)**

NDA Firm: **Hoechst Marion Roussel**

Date of Approval of NDA Insert and supplement #: **8/24/99 (S-027)**

Has this been verified by the MIS system for the NDA? **Yes**

Was this approval based upon an OGD labeling guidance? **No**

Basis of Approval for the Container Labels: **side-by-sides and container labels in file folder**

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?	X		
Has the name been forwarded to the Labeling and Nomenclature Committee? YES If so, what were the recommendations? If the name was unacceptable, has the firm been notified? NAME FOUND ACCEPTABLE	X		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		x	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	

Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X	X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

- To which USP Drug Release test does this drug product comply? If it is a non-USP drug release test the firm must place "USP Drug Release test pending." In the DESCRIPTION section. The firm has indicated that this drug product complies with USP Drug Release Test # 3
- I have e-mailed A. Langowski regarding the question of whether the firm has submitted all the materials/data regarding the following: The firm did stability testing on the 30s container size with a screw-cap but they will only be marketing a 30s size with a CRC. Andrew has stated that so long as they do stability testing on the container with the CRC that they will be okay and they have committed to do this.

FOR THE RECORD: (portions taken from previous review)

- Insert labeling based on the approved insert labeling of Cardizem[®] CD, revised May 1999, approved 8/24/99 (NDA 20-062/S-027).
- There are 6 patents (2 are use patents) for this drug product - 1/16/07, 3/26/08, 5/20/11, 11/14/11, 5/20/11 and 8/8/12 and no exclusivities. The firm believes they will not be infringing any patents [paragraph IV].
- The inactives are accurately listed in the DESCRIPTION section.

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 76-151

Date of Submission: October 20, 2003

Applicant's Name: TorPharm

Established Name: Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-Day Dosage) 120 mg, 180 mg, 240 mg, and 300 mg

Labeling Deficiencies:

1. GENERAL COMMENT

Please describe how your container label/insert labeling will accompany the product. Be explicit.

2. CONTAINER 30s, 90s and 500s

See GENERAL COMMENT above.

3. INSERT

a. GENERAL COMMENTS

i. See GENERAL COMMENT above.

ii. As a result of a recent revision to the labeling of the reference listed drug, Cardizem CD[®], approved March 21, 2003, please revise your labeling as instructed below:

b. PRECAUTIONS

i. Drug Interactions

A). Revise the second paragraph of this subsection as follows:

As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem is both a substrate and an inhibitor of the cytochrome P-450 3A4 enzyme system. Other drugs that are specific substrates, inhibitors, or inducers of this enzyme system may have a significant impact on the efficacy and side effect profile of diltiazem. Patients taking other drugs that are substrates of CYP450 3A4, especially patients with renal and/or hepatic impairment, may require dosage adjustment when starting or stopping concomitantly administered diltiazem in order to maintain optimum therapeutic blood levels.

B). Add the following sub-subsections to immediately precede the "Beta-blockers" sub-subsection:

Buspirone

In nine healthy subjects, diltiazem significantly increased the mean

bupirone AUC 5.5 fold and C_{max} 4.1 fold compared to placebo. The $T_{1/2}$ and T_{max} of bupirone were not significantly affected by diltiazem. Enhanced effects and increased toxicity of bupirone may be possible during concomitant administration with diltiazem. Subsequent dose adjustments may be necessary during coadministration, and should be based on clinical assessment.

Quinidine

Diltiazem significantly increases the $AUC_{(0 \rightarrow \infty)}$ of quinidine by 51%, $T_{1/2}$ by 36%, and decreases its CL_{oral} by 33%. Monitoring for quinidine adverse effects may be warranted and the dose adjusted accordingly.

Rifampin

Coadministration of rifampin with diltiazem lowered the diltiazem plasma concentrations to undetectable levels. Coadministration of diltiazem with rifampin or any known CYP3A4 inducer should be avoided when possible.

Benzodiazepines

Studies showed that diltiazem increased the AUC of midazolam and triazolam by 3-4 fold and the C_{max} by 2-fold, compared to placebo. The elimination half-life of midazolam and triazolam also increased (1.5 - 2.5 fold) during coadministration with diltiazem. These pharmacokinetic effects seen during diltiazem coadministration can result in increased clinical effects (e.g., prolonged sedation) of both midazolam and triazolam.

Lovastatin

In a ten-subject study, coadministration of diltiazem (120 mg bid, diltiazem SR) with lovastatin resulted in 3-4 times increase in mean lovastatin AUC and C_{max} versus lovastatin alone; no change in pravastatin AUC and C_{max} was observed during diltiazem coadministration. Diltiazem plasma levels were significantly affected by lovastatin or pravastatin.

- ii. Add the following subsection to the end of the PRECAUTIONS section:

Geriatric Use

Clinical studies of diltiazem did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

c. ADVERSE REACTIONS

Cardiovascular - "... hypotension, myopathy, palpitations ..."

d. OVERDOSAGE

- i. Revise the third paragraph as follows:

There have been reports of diltiazem overdose in amounts ranging from 1 g to 18 g. Of cases with known outcome, most patients recovered and in cases with a

fatal outcome, the majority involved multiple drug ingestion.

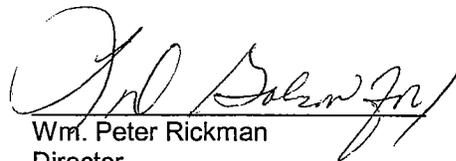
- ii. Fifth paragraph - Replace the last sentence with the following text:

The effectiveness of intravenous calcium administration to reverse the pharmacological effects of diltiazem overdose has been inconsistent. In a few reported cases, overdose with calcium channel blockers associated with hypotension and bradycardia that was initially refractory to atropine became more responsive to atropine after the patients received intravenous calcium. In some cases intravenous calcium has been administered (1 g calcium chloride or 3 g calcium gluconate) over 5 minutes, and repeated every 10-20 minutes as necessary. Calcium gluconate has also been administered as a continuous infusion at a rate of 2 g per hour for 10 hours. Infusions of calcium for 24 hours or more may be required. Patients should be monitored for signs of hypercalcemia.

Please revise your insert labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address – <http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm. Peter Rickman

Director

Division of Labeling and Program Support

Office of Generic Drugs

Center for Drug Evaluation and Research

APPROVAL SUMMARY

Was this approval based upon a petition? No
 What is the RLD on the 356(h) form: Cardizem® CD
 NDA Number: 20-062
 NDA Drug Name: Cardizem® CD (Diltiazem Hydrochloride Extended-release Capsules USP)
 NDA Firm: Hoechst Marion Roussel
 Date of Approval of NDA Insert and supplement #: 3-21-03 (S-025)
 Has this been verified by the MIS system for the NDA? Yes
 Was this approval based upon an OGD labeling guidance? No
 Basis of Approval for the Container Labels: side-by-sides and container labels in file folder
 Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter? YES - labeling has "(Once-a-day dosage)"	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? YES If so, what were the recommendations? NAME FOUND ACCEPTABLE If the name was unacceptable, has the firm been notified?			
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns? NEED CRC FOR 30s CONTAINER SIZE		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? YES - must include drug release test. If any, does ANDA meet them? YES	X	X	

Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

To which USP Drug Release test does this drug product comply? If it is a non-USP drug release test the firm must place "USP Drug Release test pending." in the DESCRIPTION section. This drug product complies with USP Drug release Test #3

FOR THE RECORD: (portions taken from previous review)

1. Insert labeling based on the approved insert labeling of Cardizem® CD, approved 3/21/03 (NDA 20-062/S-025).
2. There are 6 patents (2 are use patents) for this drug product - 1/16/07, 3/26/08, 5/20/11, 11/14/11, 5/20/11 and 8/8/12 and no exclusivities. The firm believes they will not be infringing any patents [paragraph IV].

Patent Data – 20-062

No	Expiration	Use Code	Use	File	
4894240	1-16-07			IV	None
5002776	3-26-08			IV	None
5286497	5-20-11			IV	None
5364620	11-14-11	U-3	Treatment of hypertension	IV	None
5439689	8-8-12	U-107	Treatment of hypertension and angina pectoris	IV	None
5470584	5-20-11			IV	None

Since the firm has made paragraph IV certifications to all the patents the generic labeling should not vary from the RLD. No revisions necessary from RLD.

Exclusivity Data - 20-062

Code/sup	Expiration	Use Code	Description	Labeling Impact
none				none

3. The inactives are accurately listed in the DESCRIPTION section.
4. TorPharm is the sole manufacturer.
5. The capsule descriptions are accurately reflected in the HOW SUPPLIED section.
6. The containers are all made of HDPE (light resistant). I have mentioned to the firm that their 30s container sizes should have CRC lids. The firm has stated that the 30s container size will be marketed with CRC lids.
7. Marketing

RLD - 120 mg, 180 mg, 240 mg, 300 mg: 30s, 90s & UD 100s
360 mg: 90s
ANDA -120 mg, 180 mg, 240 mg, 300 mg: 30s, 90s, 500s

8. Storage/dispensing recommendations:

USP: Preserve in tight containers

RLD: Store at CRT 15°-30°C(59°-86°F). Avoid excess humidity.

ANDA: Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].

USP: Dispense in tight containers

ANDA: Dispense in tight, light-resistant container [see USP].

9. USP labeling requirements

Indicate the Drug release test with which the product complies. I have mentioned this to the chemist and to the firm. The firm needs to put the statement "USP Drug release test pending." in the DESCRIPTION section if they do not meet any of the approved USP Drug Release tests. The firm has put "USP Drug Release Test #3" as the last sentence in the DESCRIPTION section with the October 20, 2003 submission.

10. We had decided that in the OVERDOSAGE section the words _____ should be replaced by "norepinephrine".

11. Generic firms have been asked to place the text (once-a-day dosage) in conjunction with the established name.

12. TorPharm is the manufacturer [see chem. review # 2 - vol 3.1].

Date of Review: 10-28-03

Date of Submission: 10-20-03

Primary Reviewer: Adolph Vezza

Date:

A. Vezza

11/4/03

Team Leader: Lillie Golson

Date:

Lillie Golson

11/4/03

cc: ANDA: 76-151
DUP/DIVISION FILE
HFD-613/AVezza/LGolson (no cc)
aev/10/28/03|V:\FIRMSNZ|TORPHARMLTRS&REV76151na2.l
Review

APPEARS THIS WAY
ON ORIGINAL

**APPROVAL SUMMARY
 REVIEW OF PROFESSIONAL LABELING
 DIVISION OF LABELING AND PROGRAM SUPPORT
 LABELING REVIEW BRANCH**

ANDA Number: **76-151** Date of Submission: **December 10, 2003**
 Applicant's Name: **TorPharm** Proprietary Name: **Dilt CD**
 Established Name: **Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-Day Dosage) 120 mg, 180 mg, 240 mg, and 300 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? **YES**
 Container Labels/ Professional Package Insert Labeling: **30s, 90s and 500s**
Satisfactory in FPL as of the December 10, 2003 submission.

- 120 mg - 30s [vol 6.1 - # 209106]
- 90s [vol 6.1 - # 213180]
- 500s [vol 6.1 - # 209117]
- 180 mg - 30s [vol 6.1 - # 209136]
- 90s [vol 6.1 - # 213193]
- 500s [vol 6.1 - # 209121]
- 240 mg - 30s [vol 6.2 - # 209094]
- 90s [vol 6.2 - # 213172]
- 500s [vol 6.2 - # 209099]
- 300 mg - 30s [vol 6.2 - # 209105]
- 90s [vol 6.2 - # 213177]
- 500s [vol 6.2 - # 209109]

Revisions needed post-approval: container - ensure that the strength is legible on the main panel particularly the 180 mg strength --- PI - 120 mg [500s] - ADVERSE REACTIONS - Relocate the word "myopathy" from the "Cardiovascular" subsection to after the word "retinopathy" in the last paragraph. HOW SUPPLIED - Further differentiate the 180 mg and 240 mg capsules - the description states they will only be differentiated by an imprint code ("APO 008" vs. "APO 009") - color scheme is the same

APPROVAL SUMMARY

Was this approval based upon a petition? **No**
 What is the RLD on the 356(h) form: **Cardizem® CD**
 NDA Number: **20-062**
 NDA Drug Name: **Cardizem® CD (Diltiazem Hydrochloride Extended-release Capsules USP)**
 NDA Firm: **Hoechst Marion Roussel**
 Date of Approval of NDA Insert and supplement #: **3-21-03 (S-025)**
 Has this been verified by the MIS system for the NDA? **Yes**
 Was this approval based upon an OGD labeling guidance? **No**
 Basis of Approval for the Container Labels: **side-by-sides and container labels in file folder**
 Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N/A
Different name than on acceptance to file letter? YES - labeling has "(Once-a-day dosage)"	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	

Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? YES If so, what were the recommendations? NAME FOUND ACCEPTABLE - 2-26-04	X		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns? NEED CRC FOR 30s CONTAINER SIZE		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? YES - must include drug release test. If any, does ANDA meet them? YES	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

To which USP Drug Release test does this drug product comply? If it is a non-USP drug release test the firm must place "USP Drug Release test pending." in the DESCRIPTION section. This drug product complies with USP Drug release Test #3

FOR THE RECORD: (portions taken from previous review)

1. Insert labeling based on the approved insert labeling of Cardizem[®] CD, approved 3/21/03 (NDA 20-062/S-025).
2. There are 6 patents (2 are use patents) for this drug product - 1/16/07, 3/26/08, 5/20/11, 11/14/11, 5/20/11 and 8/8/12 and no exclusivities. The firm believes they will not be infringing any patents [paragraph IV].

Patent Data – 20-062

No	Expiration	Use Code	Use	File	Labeling Impact
4894240	1-16-07			IV	None
5002776	3-26-08			IV	None
5286497	5-20-11			IV	None
5364620	11-14-11	U-3	Treatment of hypertension	IV	None
5439689	8-8-12	U-107	Treatment of hypertension and angina pectoris	IV	None
5470584	5-20-11			IV	None

Since the firm has made paragraph IV certifications to all the patents the generic labeling should not vary from the RLD. No revisions necessary from RLD.

Exclusivity Data - 20-062

Code/sup	Expiration	Use Code	Description	Labeling Impact
none				none

3. The inactives are accurately listed in the DESCRIPTION section [chem. review].
4. The capsule descriptions are accurately reflected in the HOW SUPPLIED section [vol 1.19 - section XIV - pp 7289, 7335, 7381, 7427].
5. The containers are all made of HDPE (light resistant). I have mentioned to the firm that their 30s container sizes should have CRC lids. The firm has stated that the 30s container size will be marketed with CRC lids.
6. Marketing
 RLD - 120 mg, 180 mg, 240 mg, 300 mg: 30s, 90s & UD 100s
 360 mg: 90s
 ANDA -120 mg, 180 mg, 240 mg, 300 mg: 30s, 90s, 500s
7. Storage/dispensing recommendations:
 USP: Preserve in tight containers
 RLD: Store at CRT 15°-30°C(59°-86°F). Avoid excess humidity.
 ANDA: Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].

 USP: Dispense in tight containers
 ANDA: Dispense in tight, light-resistant container [see USP].
8. USP labeling requirements

Indicate the Drug release test with which the product complies. I have mentioned this to the chemist and to the firm. The firm needs to put the statement "USP Drug release test pending." in the DESCRIPTION section if they do not meet any of the approved USP Drug Release tests. The firm has put "USP Drug Release Test #3" as the last sentence in the DESCRIPTION section with the October 20, 2003 submission.

