CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-086

ADMINISTRATIVE DOCUMENTS

CDER Establishment Evaluation Report for April 07, 1998

Application: **ANDA 75086/000**
Stamp: **04-MAR-1997** Regulatory Due:
Applicant: **TAYLOR PHARMA**
1222 WEST GRAND AVE
DECATUR, IL 62525

Priority: Org Code: **600**
Action Goal: District Goal: **04-MAY-1998**
Brand Name:
Established Name: **DILTIAZEM HYDROCHLORIDE**
Generic Name:
Dosage Form: **INJ (INJECTION)**
Strength: **5 MG/ML**

FDA Contacts: **T. AMES (HFD-617) 301-827-5849 , Project Manager**
J. SIMMONS (HFD-810) 301-594-2570 , Team Leader

Overall Recommendation:

ACCEPTABLE on 27-MAY-1997 by M. EGAS (HFD-322) 301-594-0095

Establishment: **1450114**
AKORN/TAYLOR MANUFACTURIN
1222 W GRAND AVE
DECATUR, IL 62522

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **05-MAY-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE STABILITY TESTER**

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **30-APR-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**

Establishment:

DMF No:
AADA No:

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **27-MAY-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **05-MAY-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE RELEASE TESTER**

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **08-APR-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

ANDA APPROVAL SUMMARY

ANDA: 75-086 DRUG PRODUCT: Diltiazem Hydrochloride STRENGTH: 5 mg/mL

FIRM: Taylor Pharmaceuticals DOSAGE FORM: Injection

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable for all on 5/27/97.

BIO STUDY: Firm request for a waiver of *in-vivo* bioavailability test requirements pursuant to 21 CFR §320.22(b)(1) was granted on 6/13/97 by J. Lee.

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Active Ingredient:	N/A, product is compendial refer to memo dated 11/14/90 regarding Compliance Program Guidance Manual # 7346.832, code 52832 for ANDAs and AADAs.
Finish Dosage Form:	Product is not USP, but the methods used are all USP as described for active ingredient and are also in the PF (Vol. 20, #5, 1994, p. 7971-7972).

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Protocol:	Satisfactory.
Exp.Date:	24 months - 25°C ± 2°C, 3 months, one lot each container/closure system; and 2°C - 8°, 3 months, one lot each container/closure system. Lot #628D05 (5mL vial), Lot #628D07 (10 mL vial).

Same container/closure system.

LABELING: Container: Satisfactory in FPL.
Carton: Satisfactory in FPL.
Insert: Satisfactory in FPL.

STERILIZATION VALIDATION:

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):
of 5 mL vial Jnits, Lot #628D05 of 10 mL vial units, Lot #628D07), source of NDS ok

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):
of 5 mL vial Units, Lot #628D05) of 10 mL vial nits, Lot #628D07).

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:
of 5 mL vial units) and of 10 mL vial units).

CHEMIST: Norman Gregory 3/9/98 DATE: 2/20/98

SUPERVISOR: U.V. Venkataram, Ph.D. DATE: 2/20/98

3/9/98

This Approval Summary supersedes the review dated 2-24-98.

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

ANDA Number: **75-086** Date of Submission: **January 30, 1998**

Applicant's Name: **Taylor Pharmaceuticals**

Established Name: **Diltiazem Hydrochloride Injection, 5 mg/mL 5 mL and 10 mL vials**

APPROVAL SUMMARY:

Do you have 12 Final Printed Labels and Labeling? No
9 PI in blue jacket.

Container Labels: 5 mL and 10 mL
Satisfactory as of January 30, 1998 submission.

Carton Labeling: 6 x 5 mL and 6 x 10 mL
Satisfactory as of January 30, 1998 submission.

Professional Package Insert Labeling:
Satisfactory as of January 30, 1998 submission.

Revisions needed post-approval: See review dated 2-24-98.
HOW SUPPLIED - same section heading prominence.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Cardizem®

NDA Number: 20-027

NDA Drug Name: Cardizem® (Diltiazem Hydrochloride Injection)

NDA Firm: Hoechst Marion Roussel

Date of Approval of NDA Insert and supplement #: 4/2/96 (S-011)

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 labeling on file

Basis of Approval for the Carton Labeling: side by sides and labeling on file

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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	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name?		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	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			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	

	Yes	No	N.A.
Does KLD 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	
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	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
	Yes	**No**	**N.A.**
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them? SEE FTR.			
Is the product light sensitive? Yes If so, is NDA and/or ANDA in a light resistant container? IT IS IN A LIGHT RESISTANT CARTON & IS A "SINGLE USE" 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.			

FOR THE RECORD: (most of comments taken from previous review)

1. This review was based on the labeling of the listed drug CARDIZEM® (Hoechst Marion Roussel/Marion Merrell Dow Inc; Approved 4/2/96; Revised 7/95).

2. The 25 mg vial will have a blue aluminum flip-off seal while the 50 mg vial's is white. Both vials are USP Type 1 glass.

3. Every place the inactive ingredients are mentioned - water for injection is listed yet the Raw Materials Component Testing Sheet clearly states <u>sterile</u> water for injection.

The firm was asked to comment or revise. They have commented that "sterile water for injection" is used to make the product but it is used in such a fashion that it is no longer sterile (nor, they say, does it need to be) after it is used. This is satisfactory.

4. Both this ANDA and the RLD have their drug product in a 6 x 5 mL and 6 x 10 mL packaging configuration.

5. There are no patents or exclusivities that pertain to this drug product.

6. Storage/Dispensing

USP: Not the subject of a USP monograph.

NDA: Store under refrigeration 2°-8°C (36°-46°F). Do not freeze. May be stored at room temperature for up to 1 month. Destroy after 1 month at room temperature.

ANDA: Store under refrigeration 2° to 8°C (36° to 46°F). Do not freeze. May be stored at room temperature for up to 1 month. Destroy after 1 month at room temperature.

7. All inactive ingredients are listed in the DESCRIPTION section, however, see FTR #3 above.

8. The firm has agreed to make all of the changes as stated in our labeling review dated 2-24-98 (faxed to the firm the same day) immediately post-approval (as a SS-CBE) but before they place the drug product on the market. They have faxed a letter stating these commitments to their ANDA 75-086 (hard copy to follow via mail system) and a desk copy to me. It seemed in order so I drafted this approval summary [SEE TELECON DATED 2-25-98].

9. This review was done with the red jacket.

Date of Review: 2-25-98 Date of Submission: 1-30-98

Primary Reviewer: Adolph Vezza /S/ Date: 2/25/98

Team Leader: Charlie Hoppes /S/ Date: 2/25/98

RECORD OF TELEPHONE CONVERSATION

Jim Baumann called me on 2-24-98 with comments on the faxed labeling deficiencies for 75-086 Diltiazem Hcl Injection of earlier in the day. He stated that he wished clarification on some of the comments and he wished to discuss the deficiencies with me and my supervisor. We set up 3 P.M. as the time he would call me back and Charlie Hoppes and I would speak with him. He called shortly after 3 and had Rick Taylor and Lou Fraser with him. After some discussion Jim asked us if we would accept a commitment from them to revise their labels post-approval but before the drug product was put out on the market. Charlie and I agreed to put this suggestion to Jerry Phillips. We told them that we would get back to them tomorrow (2-25-98). Both Jerry and Bob West were not available after our conversation. Jerry would not be back until 3-2-98 so Charlie and I asked Bob about Taylor's proposal. Charlie stated that we had done similar to this on other occasions and Bob said that he felt it would be okay so long as we had everything in writing. I called Jim on 2-25-98 and he agreed to send a fax copy to the document room and a desk copy to me of a letter outlining their commitment to not market the product til the revisions were made on their labels and labeling. Taylor is to submit a SS-CBE to the application immediately after approval. This is satisfactory.

Division of Labeling and Program Support

DATE
February 25, 1998

ANDA NUMBER
75-086

IND NUMBER

TELECON

INITIATED BY APPLICANT/ SPONSOR X **MADE BY TELE.**

X **FDA** _ **IN PERSON**

PRODUCT NAME
Diltiazem HCl Inj

FIRM NAME
Taylor Pharmaceuticals

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Jim Baumann
Reg. Affairs

TELEPHONE NUMBER
(217) 423-9715

SIGNATURE
Adolph Vezza
/S/ 2/25/98

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

ANDA Number: **75-086** Date of Submission: **January 30, 1998**

Applicant's Name: **Taylor Pharmaceuticals**

Established Name: **Diltiazem Hydrochloride Injection, 5 mg/mL 5 mL and 10 mL vials**

Labeling Deficiencies:

1. GENERAL COMMENT

   The primary expressions of strength for this drug product, 25 mg/5 mL and 50 mg/10 mL respectively, should appear before the secondary expression of strength, 5 mg/mL, and should be more prominent.

2. CONTAINER 25 mg/5 mL and 50 mg/10 mL

   a. Upon further consideration, please revise the statement of strength to appear outside of the colored box (where it will be more legible and prominent) in the following manner:

      For the 25 mg **25 mg/5 mL (5 mg/mL)** or **25 mg/5 mL (5 mg/mL)**

      For the 50 mg **50 mg/10 mL (5 mg/mL)** or **50 mg/10 mL (5 mg/mL)**

   b. Replace the "CAUTION: Federal law... statement with the symbol "**℞ only**". See Section 126 of the FDA Modernization Act of 1997.

3. CARTON 6 x 25 mg/5 mL and 6 x 50 mg/10 mL

   a. See comments above.

   b. Please ensure that the primary expression of strength appears on the back panel.

INSERT

4. Satisfactory in final print. The revision as shown in 2(b) above may be made in your first annual report, provided that it is explained in full.

Please revise your container labels and carton labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

Jerry Phillips
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: **75-086** Date of Submission: **January 30, 1998**

Applicant's Name: **Taylor Pharmaceuticals**

Established Name: **Diltiazem Hydrochloride Injection, 5 mg/mL 5 mL and 10 mL vials**

Labeling Deficiencies:

1. GENERAL COMMENT

   The primary expressions of strength for this drug product, 25 mg/5 mL and 50 mg/10 mL respectively, should appear before the secondary expression of strength, 5 mg/mL, and should be more prominent.

2. CONTAINER 25 mg/5 mL and 50 mg/10 mL

   a. Upon further consideration, please revise the statement of strength to appear outside of the colored box (where it will be more legible and prominent) in the following manner:

      For the 25 mg **25 mg/5 mL (5 mg/mL)** or **25 mg/5 mL (5 mg/mL)**

      For the 50 mg **50 mg/10 mL (5 mg/ml)** or **50 mg/10 mL (5 mg/mL)**

   b. Replace the "CAUTION: Federal law... statement with the symbol "**℞ only**". See Section 126 of the FDA Modernization Act of 1997.

3. CARTON 6 x 25 mg/5 mL and 6 x 50 mg/10 mL

   a. See comments above.

   b. Please ensure that the primary expression of strength appears on the back panel.

INSERT

4. Satisfactory in final print. The revision as shown in 2(b) above may be made in your first annual report, provided that it is explained in full.

Please revise your container labels and carton labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

_____

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY:

Do you have 12 Final Printed Labels and Labeling? No
9 PI in blue jacket.

Container Labels: 5 mL and 10 mL

Carton Labeling: 6 x 5 mL and 6 x 10 mL

Professional Package Insert Labeling:
Satisfactory as of January 30, 1998 submission.

Revisions needed post-approval: Replace "CAUTION: Federal law..." statement with "R" (for the insert). How SUPPLIED - same Section heading prominence.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Cardizem®

NDA Number: 20-027

NDA Drug Name: Cardizem® (Diltiazem Hydrochloride Injection)

NDA Firm: Hoechst Marion Roussel

Date of Approval of NDA Insert and supplement #: 4/2/96 (S-011)

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 labeling on file

Basis of Approval for the Carton Labeling: side by sides and labeling on file

---

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	

	Yes	No	N.A.
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name?		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	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			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	
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	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			

	Yes	No	N.A.
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them? SEE FTR.			
Is the product light sensitive? Yes If so, is NDA and/or ANDA in a light resistant container? IT IS IN A LIGHT RESISTANT CARTON & IS A "SINGLE USE" 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.			

FOR THE RECORD:

1. This review was based on the labeling of the listed drug CARDIZEM® (Hoechst Marion Roussel/Marion Merrell Dow Inc; Approved 4/2/96; Revised 7/95).

2. The 25 mg vial will have a blue aluminum flip-off seal while the 50 mg vial's is white. Both vials are USP Type 1 glass.

3. Every place the inactive ingredients are mentioned - water for injection is listed yet the Raw Materials Component Testing Sheet clearly states sterile water for injection. The firm was asked to comment or revise. They have commented that "sterile water for injection" is used to make the product but it is used in such a fashion that it is no longer sterile (nor, they say, does it need to be) after it is used. This is satisfactory.

4. Both this ANDA and the RLD have their drug product in a 6 x 5 mL and 6 x 10 mL packaging configuration.

5. There are no patents or exclusivities that pertain to this drug product.

6. Storage/Dispensing

   USP: Not the subject of a USP monograph.

   NDA: Store under refrigeration 2°-8°C (36°-46°F). Do not freeze. May be stored at room temperature for up to 1 month. Destroy after 1 month at room temperature.

   ANDA: Store under refrigeration 2° to 8°C (36° to 46°F). Do not freeze. May be stored at room temperature

for up to 1 month. Destroy after 1 month at room temperature.

7. All inactive ingredients are listed in the DESCRIPTION section, however, see FTR #3 above.

Date of Review: 2-24-98 Date of Submission: 1-30-98

Primary Reviewer: Adolph Vezza /S/ Date: 2/24/98

Team Leader: Charlie Hoppes /S/ Date: 2/24/98

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cc:

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

ANDA Number: **75-086** Date of Submission: **November 14, 1997**

Applicant's Name: **Taylor Pharmaceuticals**

Established Name: **Diltiazem Hydrochloride Injection, 5 mg/mL 5 mL and 10 mL vials**

Labeling Deficiencies:

1. CONTAINER 25 mg/5 mL and 50 mg/10 mL

   To be considered satisfactory in final print, labels and labeling must be of true color, true clarity, and true size. We note that the lack of resolution on your container labels makes it difficult to read the established name. Please improve the clarity of your computer generated labels or submit the actual final printed container labels.

2. CARTON

   Please note that your product comparison statement and carton and insert labeling list water for injection USP as an inactive ingredient while page 320 states that this product is **sterile** water for injection. Please comment and/or revise.

3. INSERT

   a. GENERAL COMMENT

      For insert labeling to be considered satisfactory in final print the insert text must appear on a single piece of paper.

   b. DESCRIPTION

      See comment under CARTON.

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

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CDER Establishment Evaluation Report for December 15, 1997

Application: **ANDA 75086/000**
Stamp: **04-MAR-1997** Regulatory Due:
Applicant: **TAYLOR PHARMA**
1222 WEST GRAND AVE
DECATUR, IL 62525

Priority: Org Code: **600**
Action Goal: District Goal: **04-MAY-1998**
Brand Name:
Established Name: **DILTIAZEM HYDROCHLORIDE**
Generic Name:
Dosage Form: **INJ (INJECTION)**
Strength: **5 MG/ML**

FDA Contacts: **T. AMES (HFD-617) 301-827-5849 , Project Manager**
J. SIMMONS (HFD-810) 301-594-2570 , Team Leader

Overall Recommendation:

ACCEPTABLE on 27-MAY-1997 by M. EGAS (HFD-322) 301-594-0095

Establishment: **1450114**
AKORN/TAYLOR MANUFACTURIN
1222 W GRAND AVE
DECATUR, IL 62522

DMF No:

AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 05-MAY-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:
FINISHED DOSAGE STABILITY TESTER

Establishment:

DMF No:

AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 30-APR-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:
DRUG SUBSTANCE RELEASE TESTER

Establishment:

DMF No:

AADA No:

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 27-MAY-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:
FINISHED DOSAGE MANUFACTURER

Establishment:

DMF No:

AADA No:

Responsibilities:
FINISHED DOSAGE RELEASE TESTER

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 05-MAY-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment

DMF No

AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 08-APR-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:
DRUG SUBSTANCE MANUFACTURER

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

ANDA Number: **75-086** Date of Submission: **November 14, 1997**

Applicant's Name: **Taylor Pharmaceuticals**

Established Name: **Diltiazem Hydrochloride Injection, 5 mg/mL 5 mL and 10 mL vials**

Labeling Deficiencies:

1. CONTAINER 25 mg/5 mL and 50 mg/10 mL

   To be considered satisfactory in final print, labels and labeling must be of true color, true clarity, and true size. We note that the lack of resolution on your container labels makes it difficult to read the established name. Please improve the clarity of your computer generated labels or submit the actual final printed container labels.

2. CARTON

   Please note that your product comparison statement and carton and insert labeling list water for injection USP as an inactive ingredient while page 320 states that this product is **sterile** water for injection. Please comment and/or revise.

3. INSERT

   a. GENERAL COMMENT

      For insert labeling to be considered satisfactory in final print the insert text must appear on a single piece of paper.

   b. DESCRIPTION

      See comment under CARTON.

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

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels:

Carton Labeling:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Cardizem®

NDA Number: 20-027

NDA Drug Name: Cardizem® (Diltiazem Hydrochloride Injection)

NDA Firm: Hoechst Marion Roussel

Date of Approval of NDA Insert and supplement #: 4/2/96 (S-011)

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:

Basis of Approval for the Carton Labeling:

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	
If not USP, has the product name been proposed in the PI?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name?		X	

	Yes	No	N.A.
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	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			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	
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	
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	
Does USP have labeling recommendations? If any, does ANDA meet them? SEE FTR.			

	Yes	No	N.A.
Is the product light sensitive? Yes If so, is NDA and/or ANDA in a light resistant container? IT IS IN A LIGHT RESISTANT CARTON & IS A "SINGLE USE" 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?: FYR: 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:

The USP monograph for diltiazem hydrochloride recommends storage in light-resistant containers. This drug product is in a clear glass vial - will this be a problem? How light-sensitive is it? I figure that since it is packaged in a (light-resistant?) carton of 6 and is a single use container that it should be okay.

FOR THE RECORD:

1. This review was based on the labeling of the listed drug CARDIZEM® (Hoechst Marion Roussel/Marion Merrell Dow Inc; Approved 4/2/96; Revised 7/95).

2. The 25 mg vial will have a blue aluminum flip-off seal while the 50 mg vial's is white. Both vials are USP Type 1 glass.

3. Every place the inactive ingredients are mentioned - water for injection is listed yet the Raw Materials Component Testing Sheet clearly states sterile water for injection. The firm was asked to comment or revise. They have done neither so I asked them again.

4. Both this ANDA and the RLD have their drug product in a 6 x 5 mL and 6 x 10 mL packaging configuration.

5. There are no patents or exclusivities that pertain to this drug product.

6. Storage/Dispensing

   USP: Not the subject of a USP monograph.

   NDA: Store under refrigeration 2°-8°C (36°-46°F). Do not freeze. May be stored at room temperature for up to 1 month. Destroy after 1 month at room temperature.

ANDA: Store under refrigeration 2° to 8°C (36° to 46°F). Do not freeze. May be stored at room temperature for up to 1 month. Destroy after 1 month at room temperature.

7. All inactive ingredients are listed in the DESCRIPTION section water for injection should be listed as sterile water for injection (possibly).

Date of Review: November 20, 1997 Date of Submission: 11/14/97

Primary Reviewer: Adolph Vezza Date: 11/25/97

Team Leader: Charlie Hoppes Date: 11/25/97

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cc:

IA2.L

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001.
Expiration Date: April 30, 1994.
See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT	DATE OF SUBMISSION
Taylor Pharmaceuticals	11/14/97
ADDRESS *(Number, Street, City, State and Zip Code)*	TELEPHONE NO. *(Include Area Code)*
1222 West Grand Avenue Decatur, Illinois 62525	(217) 423-9715
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
	75-086

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Diltiazem Hydrochloride Injection, 5 mg/mL	None

CODE NAME *(If any)*	CHEMICAL NAME
None	1,5-benzothiazepin-4(5H)one, 3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride, (+)-cis-.

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Injectable	Intravenous	5 mg/mL

PROPOSED INDICATIONS FOR USE

Diltiazem hydrochloride injection is intended for use in adult patients for the temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter and for the rapid conversion of paroxysmal supraventricular tachycardias (PSVT) in sinus rhythm.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:

RECEIVED
NOV 17 1997
GENERIC DRUGS

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☒ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION
Cardizem® Injectable	Marion Merrell Dow

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☒ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))* _____

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

000001

Taylor Pharmaceuticals an Akorn Co.

• generics • injectables • ophthalmics • contract services

11/18
FA noted, to chemistry reviewer for review, Hard copy to labeling reviewer for review.
11/18/97

November 14, 1997

Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: FACSIMILE AMENDMENT TO ANDA 75-086
Diltiazem Hydrochloride Injection, 5 mg/mL
5 mL and 10 mL Vials

Dear Sir/Madam:

Taylor Pharmaceuticals (an Akorn Company), a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits this Facsimile Amendment to our Abbreviated New Drug Application for Diltiazem Hydrochloride Injection, 5 mg/mL, an injectable drug intended for use in adult patients for the temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter and for the rapid conversion of paroxysmal supraventricular tachycardias (PSVT) in sinus rhythm. The reference listed drug (RLD) is Cardizem® Injectable, the subject of NDA 20-027, which is held by Marion Merrell Dow and was approved on October 24, 1991.

This amendment is in response to the FDA Deficiency Letter (Facsimile), dated October 17, 1997, listing minor deficiencies and/or comments regarding ANDA 75-086 and requesting Taylor to provide a complete response to these deficiencies as a "Facsimile Amendment".

For ease of reference, this amendment is numbered sequentially in the lower right corner so that both the text and attachments bear consecutive numbers. A table of contents is provided for additional convenience of review.

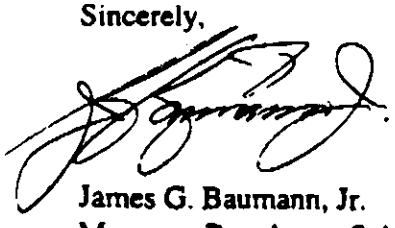
Taylor is filing an archival copy consisting of one volume (in blue folder) of this amendment and a technical review copy (in red folder) which is identical to the archival copy. An additional certified field copy (in maroon folder) was sent to the Chicago District Office.

In accordance with 21 CFR § 314.96 (b), and by reference 314.60 (c), Taylor Pharmaceuticals certifies that a true copy of this Facsimile Amendment to ANDA 75-086 for Diltiazem Hydrochloride Injection, 5 mg/mL, has been provided to the FDA Chicago

District Office. A copy of this certification with an original signature is provided with this amendment as **Attachment N.**

Should additional information be required regarding this amendment, please feel free to contact me at (217) 423-9715 or FAX (217) 428-8514.

Sincerely,



James G. Baumann, Jr.
Manager, Regulatory Submissions

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

ANDA Number: 75-086 Date of Submission: February 28, 1997

Applicant's Name: Taylor Pharmaceuticals

Established Name: Diltiazem Hydrochloride Injection, 5 mg/mL
5 mL and 10 mL vials

Labeling Deficiencies:

1. GENERAL COMMENT:

   We note you have "Taylor Pharmaceuticals" printed on all your labeling pieces without a qualifying statement. Please note that the appearance on a drug product label of a person's name without qualification is a representation that the named person is the sole manufacturer of the product. See 21 CFR 201.1(h)(2) for guidance. In your letter of February 28, 1997, you clarify that the finished drug product is manufactured for Taylor by Chesapeake Biological Laboratories, Inc. Please revise to reflect this relationship as described in 21 CFR 201.1(h)(5).

2. CONTAINER 25 mg/5 mL and 50 mg/10 mL

   a. See GENERAL COMMENT.

   b. Revise so that the routes of administration appear on the principal display panel. Note, you may relocate the place of business of manufacturer to a side panel.

   c. Revise the expression of strength to read:

      ___ mg/ ___ mL (5 mg/mL)

   d. Add the following statements to a side panel:

      Date Removed From Refrigeration: _____
      Date To Be Discarded: _____

   e. Include the statement:

      DISCARD UNUSED PORTION

3. CARTON 6 X 5 mL and 6 x 10 mL

a. See GENERAL COMMENT and comment c under CONTAINER.

b. We note your product comparison on page 19 lists sodium hydroxide **and/or** hydrochloric acid as inactive ingredients while your carton and insert labeling list sodium hydroxide **or** hydrochloric acid. Please comment and/or revise.

c. We further note that your product comparison statement and carton and insert labeling list water for injection USP as an inactive ingredient while page 320 states that this product is **sterile** water for injection. Please comment and/or revise.

d. SINGLE USE CONTAINERS (plural)

e. Revise the "Contains" statement to read "Each mL contains" and revise quantities of active and inactive ingredients as appropriate.

4. INSERT

a. GENERAL COMMENT

Italicize "*in vivo*" and "*in vitro*" throughout the rest of the insert.

b. DESCRIPTION

i. First sentence - Delete "injection".

ii. ... structural formula is:

iii. Include the molecular formula $C_{22}H_{26}N_2O_4S \cdot HCl$.

iv. Revise the molecular weight to read 450.99 as per USP 23.

v. See comments (b) and (c) under CARTON.

vi. Include an "Each mL contains" statement (see comment e under CARTON).

c. CLINICAL PHARMACOLOGY

i. Mechanism of Action - Delete "hydrochloride injection" from this subsection.

ii. Hemodynamics - Delete "injection" from the first sentence.

iii. Pharmacokinetics and Metabolism

A). First sentence

(1) Delete "injection".

(2) Delete the trailing 0 in 21.0 mg.

B). Third and fourth sentences - Delete "hydrochloride injection".

C). Third paragraph, first sentence - ... different ***oral*** diltiazem hydrochloride formulations, constant rate intravenous infusions of diltiazem hydrochloride at 3, 5, 7, and 11 mg/h are predicted to produce steady-state ... or extended-release capsules.

D). Fourth paragraph - Delete "hydrochloride" in the penultimate sentence.

E). Fifth paragraph - Delete "injection" in the first sentence

F). Sixth paragraph - Delete "hydrochloride" throughout the paragraph

d. INDICATIONS AND USAGE

Delete the extra blank line/space in the bolded paragraph.

e. WARNINGS

... (see PRECAUTIONS, Drug Interactions) ...

f. PRECAUTIONS

i. General - Delete "injection" in the first sentence.

ii. Drug Interactions, Cyclosporine - Delete the second "the" in the second paragraph.

iii. Delete "hydrochloride injection" from the

"Nursing Mothers" and "Pregnancy" subsections.

g. OVERDOSAGE

Bradycardia - ... (0.6 to 1 mg) ... Delete the trailing zeroes.

h. DOSAGE AND ADMINISTRATION

i. Delete the trailing zero in the table (1 mg/mL).

ii. Revise the heading in the table to read:

Quantity of Diltiazem Hydrochloride Injection to Add

iii. Revise as follows:

- dextrose injection 5%
- sodium chloride injection 0.9%
- dextrose (5%) and sodium chloride (0.9%) injection

i. HOW SUPPLIED

i. See GENERAL COMMENT.

ii. We encourage you to add the statement "CAUTION: Federal (USA) law prohibits dispensing without prescription."

iii. Indicate that your drug product is available in cartons of 6.

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

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

/S/

Jerry Phillips
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: 75-086 Date of Submission: February 28, 1997

Applicant's Name: Taylor Pharmaceuticals

Established Name: Diltiazem Hydrochloride Injection, 5 mg/mL 5 mL and 10 mL vials

Labeling Deficiencies:

1. GENERAL COMMENT:

   We note you have "Taylor Pharmaceuticals" printed on all your labeling pieces without a qualifying statement. Please note that the appearance on a drug product label of a person's name without qualification is a representation that the named person is the sole manufacturer of the product. See 21 CFR 201.1(h)(2) for guidance. In your letter of February 28, 1997, you clarify that the finished drug product is manufactured for Taylor by
   Please revise to reflect this relationship as described in 21 CFR 201.1(h)(5).

2. CONTAINER 25 mg/5 mL and 50 mg/10 mL

   a. See GENERAL COMMENT.

   b. Revise so that the routes of administration appear on the principal display panel. Note, you may relocate the place of business of manufacturer to a side panel.

   c. Revise the expression of strength to read:

      ___ mg/ ___ mL (5 mg/mL)

   d. Add the following statements to a side panel:

      Date Removed From Refrigeration: _____
      Date To Be Discarded: _____

   e. Include the statement:

      DISCARD UNUSED PORTION

3. CARTON 6 X 5 mL and 6 x 10 mL

a. See GENERAL COMMENT and comment c under CONTAINER.

b. We note your product comparison on page 19 lists sodium hydroxide **and/or** hydrochloric acid as inactive ingredients while your carton and insert labeling list sodium hydroxide **or** hydrochloric acid. Please comment and/or revise.

c. We further note that your product comparison statement and carton and insert labeling list water for injection USP as an inactive ingredient while page 320 states that this product is **sterile** water for injection. Please comment and/or revise.

d. SINGLE USE CONTAINERS (plural)

e. Revise the "Contains" statement to read "Each mL contains" and revise quantities of active and inactive ingredients as appropriate.

4. INSERT

a. GENERAL COMMENT

Italicize "*in vivo*" and "*in vitro*" throughout the rest of the insert.

b. DESCRIPTION

i. First sentence - Delete "injection".

ii. ... structural formula is:

iii. Include the molecular formula $C_{22}H_{26}N_2O_4S \cdot HCl$.

iv. Revise the molecular weight to read 450.99 as per USP 23.

v. See comments (b) and (c) under CARTON.

vi. Include an "Each mL contains" statement (see comment e under CARTON).

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i. Mechanism of Action - Delete "hydrochloride injection" from this subsection.

ii. Hemodynamics - Delete "injection" from the first sentence.

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A). First sentence

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(2) Delete the trailing 0 in 21.0 mg.

B). Third and fourth sentences - Delete "hydrochloride injection".

C). Third paragraph, first sentence - ... different ***oral*** diltiazem hydrochloride formulations, constant rate intravenous infusions of diltiazem hydrochloride at 3, 5, 7, and 11 mg/h are predicted to produce steady-state ... or extended-release capsules.

D). Fourth paragraph - Delete "hydrochloride" in the penultimate sentence.

E). Fifth paragraph - Delete "injection" in the first sentence

F). Sixth paragraph - Delete "hydrochloride" throughout the paragraph

d. INDICATIONS AND USAGE

Delete the extra blank line/space in the bolded paragraph.

e. WARNINGS

... (see PRECAUTIONS, Drug Interactions) ...

f. PRECAUTIONS

i. General - Delete "injection" in the first sentence.

ii. Drug Interactions, Cyclosporine - Delete the second "the" in the second paragraph.

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Bradycardia - ... (0.6 to 1 mg) ... Delete the trailing zeroes.

h. DOSAGE AND ADMINISTRATION

i. Delete the trailing zero in the table (1 mg/mL).

ii. Revise the heading in the table to read:

Quantity of Diltiazem Hydrochloride Injection to Add

iii. Revise as follows:

•dextrose injection 5%
•sodium chloride injection 0.9%
•dextrose (5%) and sodium chloride (0.9%) injection

i. HOW SUPPLIED

i. See GENERAL COMMENT.

ii. We encourage you to add the statement "CAUTION: Federal (USA) law prohibits dispensing without prescription."

iii. Indicate that your drug product is available in cartons of 6.

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

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels:

Carton Labeling:
Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Cardizem®

NDA Number: 20-027

NDA Drug Name: Cardizem® (Diltiazem Hydrochloride Injection)

NDA Firm: Hoechst Marion Roussel

Date of Approval of NDA Insert and supplement #: 4/2/96 (S-011)

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:

Basis of Approval for the Carton Labeling:

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	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name?		X	

	Yes	No	N.A.
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	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			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		
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	
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	
Does USP have labeling recommendations? If any, does ANDA meet them? SEE FTR.			

Is the product light sensitive? Yes If so, is NDA and/or ANDA in a light resistant container? IT IS IN A LIGHT RESISTANT CARTON & IS A "SINGLE USE" 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?: PTE: 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:

1. The USP monograph for diltiazem hydrochloride recommends storage in light-resistant containers. This drug product is in a clear glass vial - will this be a problem? How light-sensitive is it? I figure that since it is packaged in a (light-resistant?) carton of 6 and is a single use container that it should be okay. *I concur*

2. See comment 3(b). *Fine with me.* *4/4/97*

FOR THE RECORD:

1. This review was based on the labeling of the listed drug CARDIZEM® (Hoechst Marion Roussel/Marion Merrell Dow Inc; Approved 4/2/96; Revised 7/95).

2. The 25 mg vial will have a blue aluminum flip-off seal while the 50 mg vial's is white. Both vials are USP Type 1 glass.

3. Every place the inactive ingredients are mentioned - water for injection is listed yet the Raw Materials Component Testing Sheet clearly states sterile water for injection. The firm has been asked to comment.

4. Both this ANDA and the RLD have their drug product in a 6 x 5 mL and 6 x 10 mL packaging configuration.

5. There are no patents or exclusivities that pertain to this drug product.

6. Storage/Dispensing

   USP: Not the subject of a USP monograph.

   NDA: Store under refrigeration 2°-8°C (36°-46°F). Do not freeze. May be stored at room temperature for up to 1 month. Destroy after 1 month at room temperature.

ANDA: Store under refrigeration 2° to 8°C (36° to 46°F). Do not freeze. May be stored at room temperature for up to 1 month. Destroy after 1 month at room temperature.

7. All inactive ingredients are listed in the DESCRIPTION section water for injection should be listed as sterile water for injection (possibly) and likely that the acid/base present should be listed as sodium hydroxide and/or hydrochloric acid.

8. is the manufacturer for this drug product not Taylor Pharmaceuticals as is implied throughout the labels and labeling. See GENERAL COMMENT.

Date of Review: August 22, 1997 Date of Submission: 2/28/97

Primary Reviewer: Adolph Vezza Date:

/S/ 8/28/97

Team Leader: Charlie Hoppes Date:

/S/ 8/28/97

CDER Establishment Evaluation Report
for April 08, 1997

Application: **ANDA 75086/000**
Stamp: **04-MAR-1997** Regulatory Due:
Applicant: **TAYLOR PHARMA**
1222 WEST GRAND AVE
DECATUR, IL 62525

Priority:
Action Goal:
Brand Name:
Established Name: **DILTIAZEM HYDROCHLORIDE**
Generic Name:
Dosage Form: **INJ (INJECTION)**
Strength: **5 MG/ML**

Org Code: **600**
District Goal: **04-MAY-1998**

FDA Contacts: **T. AMES (HFD-617) 301-594-0305 , Project Manager**
J. SIMMONS (HFD-647) 301-594-0305 , Team Leader

Overall Recommendation:

Establishment: **1450114**
AKORN/TAYLOR MANUFACTURIN
1222 W GRAND AVE
DECATUR, IL 62522

DMF No:

Responsibilities:
FINISHED DOSAGE STABILITY TESTER

Establishment:

o:

Responsibilities:
DRUG SUBSTANCE RELEASE TESTER

Establishment:

DMF No:

Responsibilities:
FINISHED DOSAGE MANUFACTURER

Establishment:

Responsibilities:
FINISHED DOSAGE RELEASE TESTER

Establishment:

Responsibilities:

DRUG SUBSTANCE MANUFACTURER

RECORD OF TELEPHONE CONVERSATION/MEETING

I spoke w/ Jim Bauman and requested a patent certification which wasn't in the application. I explained that even if there isn't a patent listed, there needs to be a patent certification per the regulations. He said he will fax one in shortly.

DATE

April 8, 1997

ANDA NUMBER

75-086

IND NUMBER

TELECON

INITIATED BY _ APPLICANT/ SPONSOR _X FDA

MADE X BY TELE. _ IN PERSON

PRODUCT NAME

Diltiazem Hydrochloride Injection, 5 mg/mL

FIRM NAME

Taylor Pharmaceuticals

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

Jim Baumann
(217) 423-9715

TELEPHONE NUMBER

SIGNATURE

737