CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74910

ADMINISTRATIVE DOCUMENTS

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

Date of Review: September 17, 1996

Date of Submission: June 12, 1996

Reviewer: Charlie Hoppes

Secondary Reviewer: Adolph Vezza

ANDA Number: 74-910 Review Cycle: 1

Applicant's Name [as seen on 356(h)]: Mylan Pharmaceuticals Inc.

Established Name: Diltiazem Hydrochloride Extended-release Capsules USP (Twice-a-Day Dosage)*, 60 mg, 90 mg, and 120 mg.

*See F.T.R regarding the established name

LABELING DEFICIENCIES, WHICH ARE TO BE INCORPORATED WITH THE CHEMISTRY COMMENTS TO THE FIRM:

[NOTE: These deficiencies can be located on the x-drive as detailed in notes from Ted Sherwood regarding the New X-Drive]

B. LABELING DEFICIENCIES

1. GENERAL COMMENT:

Revise so that the phrase, "Twice-a-Day dosage" follows the established name of your product as below, where it appears on container labels and package insert labeling:

Diltiazem Hydrochloride Extended-release Capsules USP (Twice-a-Day Dosage)

2. CONTAINER

a. See GENERAL comment.

b. Please include the following statement on the container label:

Diltiazem Hydrochloride Extended-release Capsules USP which exhibit different pharmacokinetics are also marketed. Please confirm you are dispensing the prescribed formulation.

iii. Pediatric Use

...in pediatric patients...

e. ADVERSE REACTIONS (Other - second paragraph)

i. Make the following revisions in the first sentence:

...diltiazem: allergic reactions, alopecia, angioedema (including facial or periorbital edema), asystole, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), extrapyramidal...

ii. Make the following revision in the penultimate sentence, "...generalized rash, some characterized...".

f. OVERDOSAGE OR EXAGGERATED RESPONSE

i. Add the following sentence as the penultimate sentence of the sixth paragraph:

Limited data suggest that plasmapheresis or charcoal hemoperfusion may hasten diltiazem elimination following overdose.

ii. Make the following revision in the penultimate sentence, "...or norepinephrine bitartrate...".

g. DOSAGE AND ADMINISTRATION

Make the following revision in the second sentence, "...therefore, dosage adjustments...".

h. HOW SUPPLIED

i. Include the established name of the product in this section, e.g., Diltiazem hydrochloride extended-release capsules (twice-a-day dosage) are supplied as follows:

ii. We encourage the inclusion of the statement appearing under CONTAINER (b) in this section.

Please prepare and submit final print container labels and final printed (or printers proof) package insert labeling. Please note that final printed insert labeling is not required for tentative approval of an application if it is granted with more than 90 days remaining from the date when full approval can be considered. We will accept final

"printers proof" for the insert only.

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.

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

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? 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?			
Has the name been forwarded to the Labeling and Nomenclature Committee? 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?		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? See FTR		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling(continued)	Yes	No	N.A.
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	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			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?		?	
Does USP have labeling recommendations? If any, does ANDA meet them?		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.			

NOTE TO THE CHEMIST:

Does the firm meet USP "tight container" requirements? 11/Jul/96

FOR THE RECORD:

1. This labeling review was based on the approved labeling of the listed drug CARDIZEM® SR (Approved May 28, 1996; Revised July 1995). The reviewer also referred to a 9/95 labeling guidance for direction. Although this guidance was never finalized, it provided insight in some areas.

2. There are no exclusivities for this drug product.

3. Patent 4721619 for diltiazem hydrochloride; CARDIZEM SR expires on January 26, 2005. This has been verified in the 16th ed. of the Orange Book and the 6th supplement.

4. The innovator packages the product in bottles of 100 for the 60 mg, 90 mg and 120 mg strengths. It is also available in unit dose 100's. The applicant proposes bottles of 100 for each strength.

5. Diltiazem Hydrochloride Extended-release Capsules are available from Marion Merrell Dow in two basic formulations with different dosing intervals.

It is essential to differentiate between the two Extended-release formulations in the insert labeling and on the container labels.

We have decided that we will differentiate between the two product formulations with the use of Twice-a-Day and Once-a-Day. One of these statements must appear on all labels/labeling, although the statement is not part of the established name.

Furthermore since both extended-release formulations are available in a 120 mg capsule it is imperative to alert the practitioner to assure they have selected the correct product. Thus the following phrase should appear on the container label of all extended-release products:

Diltiazem Hydrochloride Extended-release Capsules which exhibit different pharmacokinetics are also marketed. Please confirm you are dispensing the prescribed formulation.

[NOTE: This note will also serve to alert the practitioner to the various extended release formulations available.] This issue of product differentiation was discussed among Carol Zimmermann, Yana Mille, Don Hare and Jerry Phillips. Everyone was in agreement.

6. Dispensing -

USP:	Preserve in tight containers
NDA:	Dispense in a tight, light-resistant container as defined in the USP.
ANDA:	Dispense in a tight, light-resistant container as defined in the USP using a child resistant closure.

Storage -

NDA:	Store at CRT 15-30°C (59-86°F)
ANDA:	Store at CRT 15-30°C (59-86°F) - as seen on package insert. Firm has been asked to revise container labels [store at CRT 20-25°C

(68-77°F)] to be consistent with the insert.

7. Components/Composition

The inactive ingredients listed in the DESCRIPTION section of the draft insert labeling are consistent with the listing of inactive ingredients appearing on pages 5021-5029 of this submission.

8. The firm states (DESCRIPTION section) that they will meet USP Drug Release Test 4. This test appears in the third supplement to USP 23.

9. Based on the following FOR THE RECORD it has been decided not to include the referenced sentence in the labeling unless it is supported by the BIO study:

> On September 25, 1991, Dr. Dighe and Kent Johnson discussed the Clinical Pharmacokinetics subsection for this Extended-release preparation. The following sentence (Diltiazem is absorbed from the capsule formulation to about 92% of a reference solution...) will not be given away. We will evaluate the AUC of each study. If close, we will use the same language. Dr. Dighe was to have written a single dose leg to the BIO study [generic SR vs soln (or tab)] - See FTR in drug file folder.

No study comparing the applicant's product to solution was conducted. Currently there is no requirement from the Division of Bioequivalence that such a study be conducted. For these reasons we will request the firm to delete the first sentence of last paragraph in CLINICAL PHARMACOLOGY.

Bio studies - Mylan conducted the following studies:

- 120 mg Fasting to steady state
- 120 mg Postprandial
- Dissolution studies comparing 60 mg, 90 mg and 120 mg

10. Although it is not possible to determine in draft, the firm commits to differentiation of strengths on container labels by use of different colors.

11. Capsule imprint descriptions appearing in the HOW SUPPLIED section are consistent with those appearing on page 5022 of this submission.

/S/
Reviewer

10/3/96
Date

/S/
Secondary Reviewer

10/3/96
Date

/S/
Team Leader
Labeling Review Branch

10/3/96
Date

ANDA 74-910
Division File
HFD-613\CHOPPES\AVEZZA\JGRACE (no cc)

Review

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

ANDA Number: 74-910 Date of Submission: January 15, 1997

Applicant's Name: Mylan Pharmaceuticals, Inc.

Established Name: Diltiazem Hydrochloride Extended-release Capsules (Twice-a-Day Dosage), 60 mg, 90 mg, and 120 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

Nine copies of each piece appear in the blue jacket (vol. 2.1). This is sufficient.

Container Labels (100's):

Satisfactory in FPL, January 15, 1997, submission.

Professional Package Insert Labeling:

Satisfactory in FPL, January 15, 1997, submission.

Revisions needed post-approval:

A. CONTAINER

If possible, the firm should revise to make the statement to the dispenser regarding products with other pharmacokinetics more prominent. The text gets lost where it is and the provider is not used to looking for this statement.

not a required statement

B. INSERT (PRECAUTIONS, Drug Interactions, *Anesthetics*)

...conductivity, and automaticity... ("automaticity" rather than

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 19-471

NDA Drug Name: Cardizem® SR Capsules

NDA Firm: Hoechst Marion Roussel, Inc.

Date of Approval of NDA Insert and supplement #: May 28, 1996: 19-471/S-024

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: Cardizem® SR Capsules

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? 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?			
Has the name been forwarded to the Labeling and Nomenclature Committee? 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?		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? See FTR		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling (continued)	**Yes**	**No**	**N.A.**
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	
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Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
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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?		?	
Does USP have labeling recommendations? If any, does ANDA meet them?		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	
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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.			

FOR THE RECORD:

1. This labeling review was based on the approved labeling of the listed drug CARDIZEM® SR (Approved May 28, 1996; Revised July 1995). The reviewer also referred to a 9/95 labeling guidance for direction. Although this guidance was never finalized, it provided insight in some areas.

2. There are no exclusivities for this drug product.

3. Patent 4721619 for diltiazem hydrochloride; CARDIZEM SR expires on January 26, 2005. This has been verified in the 16th ed. of the Orange Book and the 6th supplement. The applicant originally filed a Paragraph III Certification but amended to a Paragraph IV Certification, 8/13/96.

4. The innovator packages the product in bottles of 100 for the 60 mg, 90 mg and 120 mg strengths. It is also available in unit dose 100's. The applicant proposes bottles of 100 for each strength.

5. Diltiazem Hydrochloride Extended-release Capsules are available from Marion Merrell Dow in two basic formulations with different dosing intervals.

   It is essential to differentiate between the two Extended-release formulations in the insert labeling and on the container labels.

   We have decided that we will differentiate between the two product formulations with the use of Twice-a-Day and Once-a-Day. One of these statements must appear on all labels/labeling, although the statement is not part of the established name.

Furthermore since both extended-release formulations are available in a 120 mg capsule it is imperative to alert the practitioner to assure they have selected the correct product. Thus the following phrase should appear on the container label of all extended-release products:

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[NOTE: This note will also serve to alert the practitioner to the various extended release formulations available.] This issue of product differentiation was discussed among Carol Zimmermann, Yana Mille, Don Hare and Jerry Phillips. Everyone was in agreement.

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ANDA:	Store at CRT 15-30°C (59-86°F) - as seen on package insert. Firm has been asked to revise container labels [store at CRT 20-25°C (68-77°F)] to be consistent with the insert.

7. Components/Composition

The inactive ingredients listed in the DESCRIPTION section of the draft insert labeling are consistent with the listing of inactive ingredients appearing on pages 5021-5029 of the 6/12/96, submission.

8. The firm states (DESCRIPTION section) that they will meet USP Drug Release Test 4. This test appears in the third supplement to USP 23.

9. Based on the following FOR THE RECORD it has been decided not to include the referenced sentence in the labeling unless it is supported by the BIO study:

> On September 25, 1991, Dr. Dighe and Kent Johnson discussed the Clinical Pharmacokinetics subsection for this Extended-release preparation. The

following sentence (Diltiazem is absorbed from the capsule formulation to about 92% of a reference solution...) will not be given away. We will evaluate the AUC of each study. If close, we will use the same language. Dr. Dighe was to have written a single dose leg to the BIO study [generic SR vs soln (or tab)] - See FTR in drug file folder.

No study comparing the applicant's product to solution was conducted. Currently there is no requirement from the Division of Bioequivalence that such a study be conducted. For these reasons we will request the firm to delete the first sentence of last paragraph in CLINICAL PHARMACOLOGY.

Bio studies - Mylan conducted the following studies:

- 120 mg Fasting to steady state
- 120 mg Postprandial
- Dissolution studies comparing 60 mg, 90 mg and 120 mg

10. The firm has differentiated the strengths on container labels by use of different colors.

11. Capsule imprint descriptions appearing in the HOW SUPPLIED section are consistent with those appearing on page 5022 of the 6/12/96, submission.

Date of Review: February 21, 1997

Date of Submission: January 15, 1997

Primary Reviewer: /S/ **Date:** 2/21/97

Team Leader: /S/ **Date:** 2/24/97

CC:

ANDA 74-910
DUP/DIVISION FILE
HFD-613/CHOPPES/JGRACE (no cc)

Review

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

Diltiazem Hydrochloride ER Capsules	Mylan
60, 90 and 120 mg Capsules	Morgantown, WV
ANDA #74-910	Submission Date:
Reviewer: Moo Park	June 12, 1996; September 12, 1996

REF PRODUCT	Cardizem[R] SR, Hoechst Marion Roussel, 120 mg capsules
BE STUDY DESIGN	• An open-label randomized, two-way crossover bioequivalence study to compare the relative bioavailability of diltiazem extended release (ER) 120 mg capsules manufactured by MYLAN to that achieved by Cardizem[R] SR, Hoechst Marion Roussel, 120 mg capsules under fasting and steady-state conditions. Fasting and steady-state studies were combined into one 8-day study. • An open-label randomized, three-way crossover bioequivalence study to compare the relative bioavailability of diltiazem extended release (ER) 120 mg capsules manufactured by MYLAN to that achieved by Cardizem[R] SR, Hoechst Marion Roussel, 120 mg capsules under nonfasting conditions.
STUDY SITE	Clinical study: Clinical and Pharmacologic Research Morgantown, WV Analytical: Mylan Pharmaceuticals Morgantown, WV

STUDY SUMMARY	1. **Study under Single Dose Fasting and Multiple Dose Steady-State Conditions (#9559)**: Twenty-eight healthy male volunteers were accepted for entry into the clinical phase of the study. Twenty-four subjects successfully completed both phases of the clinical portion of the study. Pharmacokinetic and statistical analyses were performed on the data for 23 subjects. **Under single dose fasting conditions**, the 90% confidence intervals of LAUCT, LAUCI and LCMAX for diltiazem, desacetyldiltiazem and desmethyldiltiazem were all within the acceptable range of 80-125. **Under steady-state conditions**, the 90% confidence intervals of LAUCT, LCAVG, LCMAX, and LCMIN for diltiazem, desacetyldiltiazem and desmethyldiltiazem were all within the acceptable range of 80-125. 2. **Study under Nonfasting Conditions (#9572):** Twenty-three healthy male volunteers were accepted for entry into the clinical phase of the study. Sixteen subjects successfully completed all three phases of the clinical portion of the study. **Under nonfasting conditions**, the test/reference ratios of LAUCT, LAUCI and LCMAX under nonfasting conditions for diltiazem, desacetyldiltiazem and desmethyldiltiazem were all within the acceptable range of 0.8-1.25. 3. Formulation: Three test formulations, 60 mg, 90 mg and 120 mg strengths, are proportional in active and inactive ingredients. The same granules were used to manufacture the 60 mg, 90 mg and 120 capsules. 4. There was no severe medical event which required a clinical action. 5. The batch size of the bio-batch (120 mg strength; lot #2B005L) was capsules.
BIOASSAY VALIDATION	Assay method validation data are acceptable.
DISSOLUTION	Test products (60 mg, 90 mg and 120 mg strengths) met USP dissolution specifications.
WAIVER	Waivers are granted for the 60 mg and 90 mg capsules.

INITIAL: /S/ DATE: 3/5/97
REVIEWER: Moo Park, Ph.D.
BRANCH: III

INITIAL: /S/ DATE: 3/6/97
TEAM LEADER: Ramakant M. Mhatre, Ph.D.
BRANCH: III

INITIAL: /S/ DATE: 5/2/97
DIRECTOR: Nicholas Fleischer, Ph.D.
DIVISION OF BIOEQUIVALENCE

INITIAL: _____ DATE: _____
DIRECTOR
OFFICE OF GENERIC DRUGS

RECORD OF TELEPHONE CONVERSATION

Gordon and I called Frank Sisto of Mylan to request any additional evidence that the patent holder for diltiazem (Cardizem SR Capsules), had been notified of non-infringement of their '619 patent.

Mr. Sisto of Mylan provided a letter from a law firm acting as "outside patent counsel" for Elan Corp. that acknowledges receipt of notice of non-infringement.

I believe that the above letter and the documentation of FedEx delivery satisfy the notification requirements to the patent holder, Elan Corp.

DATE
April 8, 1997

APPLICATION NUMBER
74-910

IND NUMBER

TELECON

INITIATED BY _ APPLICANT/SPONSOR X_FDA

MADE _ BY TELE. _ IN PERSON

PRODUCT NAME
diltizem ER caps

FIRM NAME
Mylan

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Frank Sisto Reg Affairs

TELEPHONE NUMBER
(304)599-2595

SIGNATURE
/S/ 4/8/97

See fax dated 4/8/97

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 27, 1996

FROM: Anna Marie H. Weikel, R.Ph., CSO /S/

SUBJECT: ANDA 74-910/Inactive Ingredient/Eudragit S100

TO: John Simmons, Ph.D., Team Leader, Branch 7

Mylan submitted an application for Diltiazem Extended Release Capsules for a formulation which contains an inactive ingredient, Eudragit S100, that is not listed in the CDER IIG.

Another firm, Biovail, recently submitted an application (ANDA 74-845) for the same drug which also contained, Eudragit S100 as an inactive ingredient. Based on the fact that Bioavail did not provide enough information about the identity of this inactive ingredient in the initial submission, it was a Refuse to File. In their recent amendment, Biovail provided additional information about Eudragit S100 which included a detailed clarification of the different terminology from supplier; and reference to an approved drug product which contains Eudragit S. Their explanation was considered satisfactory and the application was accepted for filing based on the fact that it appears, from the explanation provided, that Eudragit S100 is the same as Eudragit S, except that Eudragit S100 is the powder form. It also meets the specifications of the USP monograph for "Methacrylic Acid Copolymer" (which refers to both Eudragit L100 (Type A) and Eudragit S100 (Type B)). Methacrylic Acid Copolymer is also listed in the CDER IIG.

Based on this information, we believe that the Mylan application should be accepted for filing also.

Jss 7.3.96
cparise 7/17/96
file