

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-086

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-086

3. NAME AND ADDRESS OF APPLICANT

Taylor Pharmaceuticals
150 S. Wyckles Road
P.O. Box 1220
Decatur, IL 62525

4. LEGAL BASIS FOR SUBMISSION

In the opinion of Taylor Pharmaceuticals, and to the best of its knowledge, there is no patent in effect and there is no marketing exclusivity in effect for the listed drug.

Innovator: Marion Merrill Dow Inc. - Cardizem[®] Injectable.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Diltiazem Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm: 2/28/97 - Original.
4/8/97 - O/NC, response to phone memo.
5/15/97 - Unsolicited amendment.
11/14/97 - Response to 1st def. (chem. & labeling).
1/30/98 - Response to 2nd def. (Micro. & labeling). Subject of this review.

FDA: 4/8/97 - Phone memo, patent certification.
4/22/97 - Acknowledgment.
6/13/97 - Bio. review, waiver granted.
6/25/97 - Bio. letter, no further questions.
6/25/97 - 1st Micro. review, unacceptable.
10/17/97 - 1st def. Facsimile (chem. & labeling).
12/4/97 - 2nd Micro. review, unacceptable.
12/30/97 - 2nd def. facsimile (Micro. & labeling).
2/9/98 - 3rd Micro. review, acceptable

10. PHARMACOLOGICAL CATEGORY
Anti-anginal

11. Rx or OTC
R

12. RELATED IND/NDA/DMF(s)

(Facility, Taylor Pharmaceuticals, LoA)
(Facility, Chesapeake Biological Laboratories, LoA);
(Active, Orion Corporation Fermion, LoA);
(Facility, Applied Analytical Industries, LoA);
(Closure, The West Company, LoA).

13. DOSAGE FORM

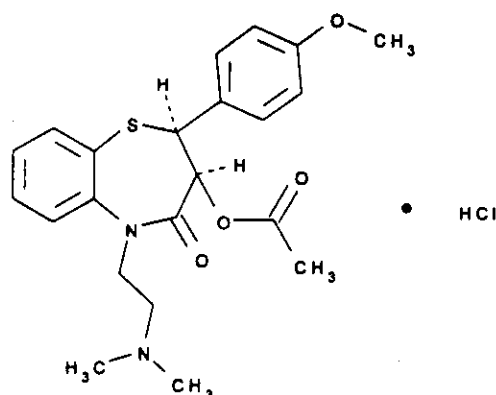
Injection (SDV)

14. POTENCY

5 mg/mL, 5 mL & 10 mL vials

15. CHEMICAL NAME AND STRUCTURE

Diltiazem Hydrochloride USP

 $C_{22}H_{26}N_2O_4S.HCl$; M.W. = 450.98

(+)-5-[2-(Dimethylamino)ethyl]-*cis*-2,3-dihydro-3-hydroxy-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one acetate (ester) monohydrochloride. CAS [33286-22-5]

16. RECORDS AND REPORTS

N/A

17. COMMENTS

DMF's, EER, Bio., Micro.. labeling, and methods validation satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval

19. REVIEWER:

Norman Gregory

DATE COMPLETED:

2/20/98

Contain Trade Secret,
Commercial/Confidential
Information and are not
releasable.

2/20/98

Chemistry Review #3

Contain Trade Secret,
Commercial/Confidential
Information and are not
releasable.

12/30/97

Chemistry Comment

#33

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-086

3. NAME AND ADDRESS OF APPLICANT

Taylor Pharmaceuticals
An Akorn Co.
1222 West Grand Avenue
Decatur, IL 62525

4. LEGAL BASIS FOR SUBMISSION

In the opinion of Taylor Pharmaceuticals, and to the best of its knowledge, there is no patent in effect and there is no marketing exclusivity in effect for the listed drug.

Innovator: Marion Merrill Dow Inc. - Cardizem[®] Injectable.

5. SUPPLEMENT(S)

N/A

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Diltiazem Hydrochloride

8. SUPPLEMENT(S) PROVIDE(S) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Firm: 2/28/97 - Original.
4/8/97 - O/NC, response to phone memo.
5/15/97 - Unsolicited amendment.
11/14/97 - Response to 1st def. (chem. & labeling). Subject of this review.

FDA: 4/8/97 - Phone memo, patent certification.
4/22/97 - Acknowledgment.
6/13/97 - Bio. review, waiver granted.
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6/25/97 - 1st Micro. review, unacceptable.
10/17/97 - 1st def. Facsimile (chem. & labeling).
12/4/97 - 2nd Micro. review, unacceptable.

10. PHARMACOLOGICAL CATEGORY

Anti-anginal

11. RX or OTC

R

12. RELATED IND/NDA/DMF(S)

13. DOSAGE FORM

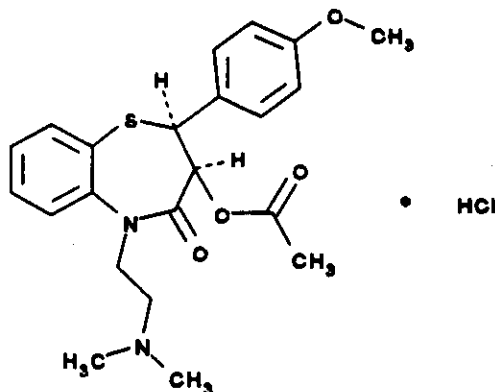
Injection (SDV)

14. POTENCY

5 mg/mL, 5 mL & 10 mL vials

15. CHEMICAL NAME AND STRUCTURE

Diltiazem Hydrochloride USP
 $C_{22}H_{26}N_2O_4S \cdot HCl$; M.W. = 450.98



(+)-5-[2-(Dimethylamino)ethyl]-cis-2,3-dihydro-3-hydroxy-2-(p-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one acetate (ester) monohydrochloride. CAS [33286-22-5]

16. RECORDS AND REPORTS

N/A

17. COMMENTS

- a. Manufacturing and Processing:
Micro. review not satisfactory.
- b. Labeling:
Container, Carton and Insert labeling not satisfactory.

DMF's, EER, Bio., and methods validation satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable (see item 17).

19. REVIEWER:

Norman Gregory

DATE COMPLETED:

12/12/97

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

12/12/97

Chemistry Review #2

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releasable.

10/17/97

Chemistry Comments

3A

1. CHEMISTRY REVIEW NO. 1
2. ANDA # 75-086
3. NAME AND ADDRESS OF APPLICANT
Taylor Pharmaceuticals
An Akorn Co.
1222 West Grand Avenue
Decatur, IL 62525
4. LEGAL BASIS FOR SUBMISSION
In the opinion of Taylor Pharmaceuticals, and to the best of its knowledge, there is no patent in effect and there is no marketing exclusivity in effect for the listed drug.

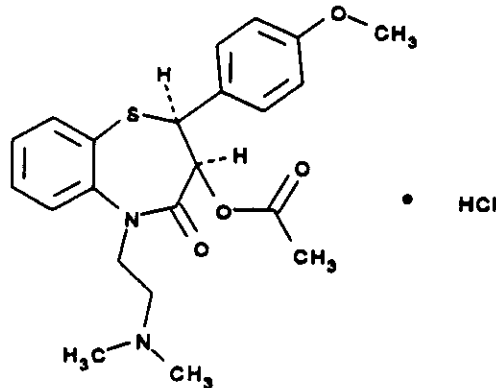
Innovator: Marion Merrill Dow Inc. - Cardizem® Injectable.
5. SUPPLEMENT(s)
N/A
6. PROPRIETARY NAME
None
7. NONPROPRIETARY NAME
Diltiazem Hydrochloride
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:
Firm: 2/28/97 - Original. Subject of this review.
4/8/97 - O/NC, response to phone memo. Subject of this review.
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FDA: 4/8/97 - Phone memo, patent certification.
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6/25/97 - Bio. letter, no further questions.
6/25/97 - 1st Micro. review.
10. PHARMACOLOGICAL CATEGORY
Anti-anginal
11. Rx or OTC
R
12. RELATED IND/NDA/DMF(s)
13. DOSAGE FORM
Injection (SDV)
14. POTENCY
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15. CHEMICAL NAME AND STRUCTURE

Diltiazem Hydrochloride USP

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(+)-5-[2-(Dimethylamino)ethyl]-*cis*-2,3-dihydro-3-hydroxy-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one acetate (ester) monohydrochloride. CAS [33286-22-5]

16. RECORDS AND REPORTS

N/A

17. COMMENTS

- a. Components and Composition:
Should be Sterile Water for Injection.
- b. Inactive Ingredients:
NOTE: Monograph for Sterile Water for Injection changed in USP 23, Supplement 5.
- c. Manufacturing and Processing:
 - (1) Micro. review not satisfactory.
 - (2) Need manufacturing site of finished product on batch record.
 - (3) Need to correct WFI (Water for Injection) to SWFI (Sterile Water for Injection).
 - (4) Need to correct the formula for calculating amount of Diltiazem Hydrochloride.
- d. Laboratory Controls (Finished Dosage Form):
Specification for Volume in Container should be 5.3 mL and 10.5 mL respectively.
- e. Stability:
 - (1) Statement about lots that fail specifications.
 - (2) Results for degradants on both stability reports at 3 month test station under refrigerated conditions appear to be typos.

- f. Labeling:
Container, Carton and Insert labeling not satisfactory.
- g. Establishment Inspection:
Request sent 4/8/97, pending.
DMF's, Bio., and methods validation satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable (see item 17).

19. <u>REVIEWER:</u>	<u>DATE COMPLETED:</u>
Norman Gregory	8/15/97 (chem)
	8/28/97 (labeling)

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Chemistry Review #1

8/15/97